CASE: LD125B NP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Vite *et al.*
APPLICATION NO: **09/084,542**
(now US Pat. 6,605,599B1)
FILED: **May 26, 1998**
FOR: **Epothilone Derivatives**

Art Unit: **1624**
Examiner: **B. Kifle**

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Commissioner for Patents
Mail Stop HATCH-WAXMAN PTE
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Alexandria, VA 22313-1450

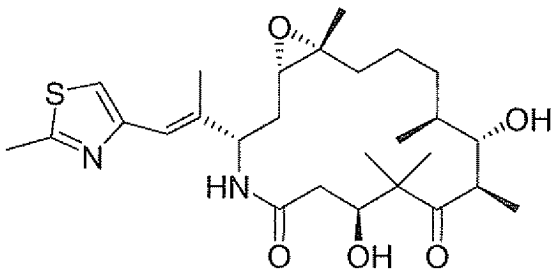
REQUEST FOR TERM EXTENSION

Sir/Madam:

The following request for an extension of the patent term is made under 35 U.S.C. §156. In accordance with this statute and 37 C.F.R. §1.740, the following information is provided, corresponding to each subsection of 37 C.F.R. §1.740(1)-(15):

(1) The approved product is IXEMPRA® (ixabepilone) for injection (15 mg supplied with DILUENT for IXEMPRA®, 8 mL; and 45 mg supplied with DILUENT for IXEMPRA®, 23.5 mL). The approved indication for IXEMPRA® (ixabepilone) comprises, in combination with capecitabine, the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane; and in monotherapy, for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine. The chemical name for ixabepilone is (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-

2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0] heptadecane-5,9-dione, and it has a molecular weight of 506.7. Ixabepilone has the following structural formula:



(2) Regulatory review occurred under the Federal Food, Drug, and Cosmetic Act, Section 505 (Title 21 of the Code of Federal Regulations).

(3) Approval to market was received on October 16, 2007.

(4) The only active ingredient in IXEMPRA® is ixabepilone. Ixabepilone has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f), and the last day on which the application could be submitted is December 17, 2007.

(6) Extension is requested of U.S. Patent 6,605,599B1, which issued on August 12, 2003 to Bristol-Myers Squibb Company, by virtue of an assignment recorded on May 26, 1998, Reel/Frame 9213/0964. The inventors of the patent are Gregory D. Vite, Soong-Hoon Kim, Robert M. Borzilleri, and James A. Johnson. The expiration date of U.S. Patent 6,605,599B1 is May 26, 2018.

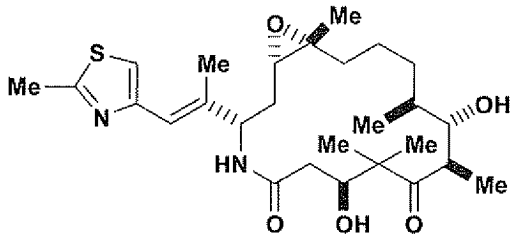
(7) A copy of U.S. Patent 6,605,599 B1 is attached.

(8) A certificate of correction issued in the patent on March 29, 2005. The certificate of correction consists of five pages, which are attached.

(9) U.S. Patent 6,605,599 B1 claims ixabepilone which is the active ingredient in the approved IXEMPRA® product. U.S. Patent 6,605,599 B1 further claims methods of treating patients by administering IXEMPRA® in the manner approved. Claims of US Pat. 6,605,599B1 which read on the approved IXEMPRA® product are claims 3, 8, 39, and 40. Claims of US Patent 6,605,599 B1 which read on methods of using the IXEMPRA® product as approved are claims 7, 9, 10, 12, 27, and 28.

(i) (a) Claim 3 of US Patent 6,605,599 B1 recites, in pertinent part, "[a] compound selected from the group of ... [1*S*-(*1R**-3R* (E),7R*,10S*,11R*,12R*,16S*)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0] heptadecane-5,9-dione," wherein the foregoing name appearing at column 50, lines 14-17, is a chemical name for ixabepilone.

(b) Claim 8 of US Patent 6,605,599 (Col. 52), recites "a compound having the formula,



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer, or stereoisomer thereof." This claim recites the chemical formula for ixabepilone, as discussed in paragraph (1), above, which is the active ingredient of the approved IXEMPRA® product.

(c) Claim 39 recites a pharmaceutical composition comprising a compound of claim 3, which includes ixabepilone as described above.

(d) Claim 40 recites a pharmaceutical composition comprising a compound of claim 8, which recites ixabepilone as described above.

(ii) (a) Claim 9 of U.S. Patent 6,605,599B1 reads on a method of using the approved IXEMPRA® product. Claim 9 recites, in pertinent part, a "method of treating breast cancer ... in a patient in need of said treatment which comprises

administering to said patient a therapeutically effective amount of a compound of claim 8." Claim 8, in turn, recites the chemical formula for ixabepilone, the active ingredient of the approved IXEMPRA® product.

(b) Claims 7, 9, 10, 12, 27, and 28 each recite methods of treating breast cancer, or methods of treating a cancer responsible to microtubule stabilization, with compounds as recited in claims 3 and 8, which read on ixabepilone.

(10)(i)(A) The effective date of the investigational new drug (IND) application for ixabepilone was July 30, 1999. The IND was submitted to the FDA on June 30, 1999. The IND was assigned the number 58,546.

(B) The new drug application for ixabepilone was submitted on April 16, 2007. The NDA for IXEMPRA® (ixabepilone) was assigned NDA 22-065

(C) NDA 22-065 was approved on October 16, 2007.

(11) The following activities were undertaken by Bristol-Myers Squibb Company during the regulatory review period:

Date	**Brief description of the activity**
June 30, 1999	Submission of initial IND application
July 15, 1999	FDA assigned IND #
July 21, 1999	CA163001 investigator information submitted
July 29, 1999	FDA provides clinical and CMC comments to IND
July 29, 1999	BMS' commitment to address clinical deficiencies
July 30, 1999	FDA acknowledgement of BMS Commitment to address deficiencies. Study may proceed.
August 5, 1999	Submission of response to request for CMC information
September 13, 1999	BMS response to clinical comments on July 29, 1999
October 14, 1999	Submission of 6 pharmacology and toxicology reports
October 15, 1999	Submission of CA163001 new investigators and administrative letter
October 19, 1999	Submission of CMC information on oral formulation
November 8, 1999	Submission of CA163001 new investigator information and Addendum No. 1 to Investigator Brochure
December 10, 1999	Submission of CA163001 protocol amendment
December 17, 1999	Submission of CMC information
March 17, 2000	Submission of CA163001 new investigator information and administrative letter, 3 pharmacology/toxicology reports, Addendum No. 2 to Investigator Brochure
March 27, 2000	Submission of CMC information and 1 pharmacology/toxicology memo
May 19, 2000	Submission of CMC information (stability reports)
June 13, 2000	Submission of 1 pharmacology/toxicology report
July 5, 2000	FDA pharmacology comment
July 13, 2000	Submission of process changes for synthesis of drug substance and addition of test and release site for drug substance
July 18, 2000	Submission of response to request for final audited versions of unaudited pharmacology/toxicology reports
August 10, 2000	Submission of CA163008 new protocol and investigator information
August 31, 2000	Submission of IND annual report covering the interval of July 1, 1999 through July 30, 2000
September 13, 2000	FDA provides CMC comments
September 20, 2000	Submission of modified storage recommendations and labels for oral formulation
September 25, 2000	Submission of response to Chemistry Reviewer's request on September 13, 2000
October 18, 2000	Submission of CA163013 and CA163015 (draft)
October 20, 2000	Request for Special Protocol Assessment CA163013

October 20, 2000	Request for Special Protocol Assessment CA163015
October 30, 2000	Email regarding SPA and FDA review of CA163013 and CA163015
November 9, 2000	Withdrawal of SPA requests for CA163013 and CA163015. Request for End of Phase 1 meeting to discuss CA163013, CA163015 and CA163012.
November 20, 2000	Submission of CMC information regarding new drug product vial size and fill volume
November 21, 2000	Submission CA163001 protocol amendment
November 27, 2000	Submission of CA163002 new protocol, administrative letter and investigators
December 13, 2000	Submission of CA163014, CA163015, CA163013 and Investigator Brochure Version 2
December 22, 2000	FDA fax with responses to BMS questions on CA163013, CA163015 and CA163012
December 22, 2000	FDA fax with biopharmaceutical comments regarding population PK analysis
January 11, 2001	Submission of oral suspension CMC information
January 15, 2001	Submission of administrative letters for CA163012, CA163013, CA163014 and CA163015 and new investigators for CA163012
February 6, 2001	Submission of CA163015 new investigators
February 9, 2001	Submission of 2 pharmacology/toxicology reports
February 14, 2001	FDA fax with clinical comments regarding endpoints
February 23, 2001	Submission of CA163002 protocol amendment and new investigators for CA163014 and CA163015
March 16, 2001	Submission of CA163011 new protocol, administrative letter and new investigators for CA163011, CA163013 and CA163014
April 9, 2001	Submission of new protocol and new investigators for CA163010 and CA163009 and administrative letter for CA163009
April 12, 2001	Submission of administrative letters for CA163009, CA163010, CA163011, CA163012, CA163013, CA163014 and CA163015, new investigators for CA163013, CA163014 and CA163015, and 1 pharmacology/toxicology report
May 8, 2001	Submission of CA163002 and CA163008 administrative letters, 1 pharmacology/toxicology report, and new investigators for CA163009, CA163010, CA163011 and CA163014
May 9, 2001	FDA fax indicating that biopharmaceutical review of February 23, 2001, BMS submission complete with no comments.
June 7, 2001	Submission of new investigators for CA163009, CA163010, CA163012, CA163013 and CA163014

July 16, 2001	Submission of protocol amendments for CA163001 and CA163010, new investigators for CA163001 and CA163013, 1 pharmacology/toxicology report
July 25, 2001	Submission of new investigators for CA163010 and Investigator Brochure Version 3
August 10, 2001	Submission of administrative letter for CA163001 and amendments for CA163009 and CA163010
August 29, 2001	Submission of protocol amendments for CA163001, CA163012 and new investigator for CA163009
September 18, 2001	BMS email to FDA regarding pediatric written request
September 25, 2001	BMS discussion with FDA via telephone regarding pediatric written request
September 27, 2001	Submission of IND annual report covering the interval of July 30, 2000 through July 29, 2001, and 2 pharmacology/toxicology reports
October 4, 2001	Submission of administrative letters for CA163001, CA163009, CA163010, protocol amendment for CA163011 and new investigators for CA163009, CA163011 and CA163014
October 15, 2001	Submission of CMC information for utility time/compatibility data, summary of 52 week stability data for 10 mg/vial and 26 week stability data for vehicle
October 24, 2001	BMS request for teleconference to review Proposed Pediatric Development Plan
October 24, 2001	BMS discussed pediatric meeting request with FDA
October 25, 2001	Submission of protocol amendment for CA163002, administrative letters and amendment for CA163009 and CA163010, administrative letters for CA163011 and CA163012, and new investigators for CA163009.
November 7, 2001	Submission of CA163031 new protocol and investigators and new investigators for CA163012
November 13, 2001	Submission of administrative letters for CA163009, CA163011 and CA163012, and protocol amendment and administrative letters for CA163014
November 15, 2001	BMS request for status of pediatric proposal
January 28, 2002	Submission of administrative letters for CA163002, CA163011, CA163012 and CA163014, investigator information for CA163011, CA163012 and CA163014, and 1 pharmacology/toxicology report
February 7, 2002	Submission of CMC information on modified process for the synthesis of drug substance and a new drug product vial size, 30 mg/vial and updates to drug substance and product sections
February 11, 2002	Submission of new protocols CA163016 and CA163022 and investigator information for CA163012 and CA163031

February 26, 2002	FDA request for BMS to submit informed consent forms for CA163016 and CA163022
February 26, 2002	Submission of informed consent forms for CA163016 and CA163022
March 11, 2002	Submission of administrative letters for CA163009 and CA163010 and new investigators for CA163011
April 8, 2002	Submission of administrative letters for CA163002, CA163011, CA163014, CA163016 and CA163022, amendment for CA163031, and investigator information for CA163010 and CA163011
April 12, 2002	FDA request that BMS review CA163016 and CA163022 to determine if they meet criteria for Clinical Trials Data Bank
April 15, 2002	Submission of 2 pharmacology/toxicology reports
April 18, 2002	Submission of amendment for CA163011 and new investigators for CA163011 and CA163031
May 24, 2002	Submission of amendment for CA163009 and investigator information for CA163031
June 21, 2002	FDA fax with Medical Reviewer's comments to CA163009 Amendment 3
June 24, 2002	Submission of BMS response to FDA's comments to CA163009 Amendment 3
July 12, 2002	Submission of new protocols and investigator information for CA163036 and CA163051
August 15, 2002	Submission of administrative letters for CA163009, CA163010, CA163011, CA163031, CA163036, CA163051 and investigator information for CA163031, CA163036, CA163009 and CA163011
August 16, 2002	Submission of administrative letters for CA163009, CA163010 CA163011, CA163031, CA163036, CA163051 and investigator information for CA163031, CA163036, CA163009 and CA163011
September 5, 2002	Submission of protocol amendment for CA163031 and investigator information for CA163036, CA163009 and CA163010
October 8, 2002	Submission of investigator information for CA163010, CA163036 and CA163051
November 13, 2002	Submission of administrative letter for CA163031 and investigator information for CA163009, CA163011, CA163031 and CA163036
November 14, 2002	Submission of CMC information for 15 mg new vial size and updates to drug substance and product sections
December 16, 2002	Submission of IND annual report covering the interval of July 30, 2001 through July 29, 2002
December 20, 2002	Submission of Investigator Brochure Version No. 4 and investigator information for CA163036 and CA163051

January 17, 2003	Submission of request for End of Phase 2 Meeting for metastatic breast cancer
February 6, 2003	FDA fax confirms End of Phase 2 Meeting on March 26, 2003
February 11, 2003	Submission of administrative letter for CA163009, CA163010, CA163012, CA163014, CA163015 and CA163031 and new investigators for CA163036
March 5, 2003	Submission of background document for End of Phase 2 Meeting for metastatic breast cancer
March 13, 2003	Submission of BMS questions for End of Phase 2 Meeting for metastatic breast cancer
March 26, 2003	FDA responded to BMS questions for End of Phase 2 Meeting
March 28, 2003	Submission of administrative letters for CA163013 and CA163014, new investigators for CA163036 and CA163051, and 2 pharmacology/toxicology reports
April 21, 2003	Submission of CA163031 protocol amendment
May 15, 2003	FDA minutes of End of Phase 2 Meeting on March 26, 2003
May 19, 2003	Submission of CA163042 new protocol and request for teleconference
May 30, 2003	FDA confirms teleconference on June 23, 2003, to discuss biopharmaceutical issues
June 2, 2003	Submission of request for Special Protocol Assessment for CA163046
June 2, 2003	Submission of request for Special Protocol Assessment for CA163048
June 10, 2003	FDA acknowledgement letter for 2 Special Protocol Assessments
June 26, 2003	BMS' minutes of biopharmaceutical meeting on June 23, 2003
July 17, 2003	FDA's comments to Special Protocol Assessment for CA163046
July 18, 2003	FDA's comments to Special Protocol Assessment for CA163048 and email with additional comment
July 23, 2003	FDA's minutes of biopharmaceutical meeting on June 23, 2003
July 30, 2003	Submission of investigator information for CA163009, CA163010 and CA163031
August 8, 2003	Submission of BMS response to FDA's comments to Special Protocol Assessment for CA163046 and CA163048
August 19, 2003	FDA confirms that BMS response for CA163048 is acceptable
August 20, 2003	Submission of CMC information of use-time stability update and updates to drug product section

August 22, 2003	FDA's minutes for July 28, 2003, teleconference regarding monotherapy indication
August 25, 2003	Submission of FACIT Manual for CA163046 and CA163048 and 6 pharmacology/toxicology reports
August 29, 2003	Submission of request for Special Protocol Assessment for CA163081
September 8, 2003	Submission of new investigators for CA163046
September 9, 2003	FDA acknowledgement letter for CA163081 Special Protocol Assessment
September 9, 2003	FDA's fax contains questions to Adverse Event Report
September 9, 2003	FDA's letter indicates the Special Protocol Assessment for CA163081 is under review
September 30, 2003	Submission of BMS' response to FDA's questions on Adverse Event Report
October 2, 2003	Submission of CA163046 protocol amendment
October 2, 2003	Submission of CA163048 protocol amendment
October 10, 2003	Submission of Independent Radiology Committee Charter for CA163046
October 23, 2003	Submission of request for CMC specific End of Phase 2 Meeting
October 28, 2003	Submission of investigator information for CA163042, CA163046 and CA163051
November 5, 2003	Submission of investigator information for CA163048
November 21, 2003	FDA comments to Special Protocol Assessment for CA163081
December 2, 2003	FDA confirmed that amendments to CA163046 and CA163048 were acceptable
December 11, 2003	Submission of BMS' responses to FDA's comments on Special Protocol Assessment for CA163081
December 18, 2003	FDA has no comments to submissions on October 2, October 3 and December 11, 2003
December 19, 2003	Submission of IND annual report covering the interval of July 30, 2002 through July 29, 2003
December 30, 2003	Submission of investigator information for CA163046 and CA163048
January 30, 2004	Submission of administrative letter for CA163081 and new investigators for CA163046, CA163048 and CA163081
January 30, 2004	Submission of interim safety data for CA163031
February 2, 2004	Submission of CMC End of Phase 2 Meeting Background document
February 13, 2004	Submission of new investigators for CA163046, CA163048 and CA163081
March 2, 2004	Submission of CA163081 protocol amendment
March 9, 2004	Submission of new investigators for CA163046, CA163048 and CA163081

March 24, 2004	FDA has no comments to submission on October 10, 2003
April 5, 2004	Submission of new investigator information for CA163046, CA163048 and CA163081
April 23, 2004	Submission of Investigator Brochure No. 5
April 26, 2004	Submission of protocol amendments for CA163009, CA163042 and CA163046, administrative letter for CA163081, and new investigator information for CA163046 and CA163048
May 19, 2004	Submission of new investigator information for CA163048 and CA163081
May 26, 2004	Submission of Independent Radiology Committee Charter for CA163081
July 1, 2004	Submission of investigator information for CA163046, CA163048 and CA163081
July 6, 2004	Submission of CA163080 new protocol and investigators
August 10, 2004	Submission of investigator information for CA163002, CA163014, CA163046 and CA163081
September 2, 2004	Submission of CA163038 new protocol and investigators
September 3, 2004	Submission of 7 pharmacology/toxicology reports
September 3, 2004	Submission of CA163046 protocol amendment
September 10, 2004	Submission of new investigators for CA163081 and CA163046
October 7, 2004	Submission of IND annual report covering the interval of July 30, 2003 through July 29, 2004
October 22, 2004	FDA provides clinical comments to submission on September 3, 2004
October 25, 2004	Submission of new investigators for CA163046, CA163048 and CA163081
November 5, 2004	Submission of 2 pharmacology/toxicology reports
November 10, 2004	Submission of final clinical study reports for CA163001, CA163002, CA163012, CA163013 and CA163015
November 23, 2004	Submission of CA163046 protocol amendment
December 8, 2004	FDA acknowledgement of November 24, 2004 submission
December 13, 2004	Submission of investigator information for CA163031, CA163046 and CA163048
January 7, 2005	FDA's comments to November 23, 2004 submission
January 11, 2005	Submission of Data Monitoring Committee Charter for CA163048
January 12, 2005	Submission of investigator information for CA163046 and CA163048
January 13, 2005	Submission of final clinical study reports for CA163008 and CA163014
February 2, 2005	Submission of 4 pharmacology/toxicology reports
February 2, 2005	FDA's comments to Special Protocol Assessment for CA163046

February 9, 2005	Submission of CA163046 protocol amendment
February 9, 2005	Submission of CA163048 protocol amendment
February 18, 2005	Submission of new investigators for CA163081
February 24, 2005	Submission of End of Phase 2 Meeting request for prostate cancer
March 3, 2005	FDA's confirms that February 9, 2005 does not effect Special Protocol Assessment agreement
March 4, 2005	FDA confirms End of Phase 2 Meeting for prostate cancer on March 29, 2005
March 10, 2005	Submission of CMC information on Cremophor-free vehicle 10.7 mL/vial
March 10, 2005	Submission of 1 pharmacology/toxicology report
March 14, 2005	Submission of background document for prostate cancer End of Phase 2 Meeting
March 15, 2005	Submission of Investigator Brochure No. 6
March 23, 2005	FDA reschedules prostate End of Phase 2 Meeting to April 15, 2005
March 25, 2005	Submission of request for review of proposed trade name
April 12, 2005	FDA responses to questions for prostate End of Phase 2 meeting
April 13, 2005	Submission of administrative letters for CA163042 and investigator information for CA163038, CA163046 and CA163048
May 11, 2005	Submission of new investigators for CA163046 and CA163048
May 25, 2005	FDA's minutes of prostate End of Phase 2 Meeting
June 16, 2005	FDA's questions to proposed trade name
June 24, 2005	FDA's addendum to minutes of prostate End of Phase 2 Meeting
July 8, 2005	Submission of administrative letter for CA163038 and investigator information for CA163046 and CA163048
July 12, 2005	Submission of new protocol, amendment and investigator for CA163102
July 13, 2005	Submission of response to FDA's questions for proposed trade name
July 19, 2005	FDA's questions to proposed trade name
July 29, 2005	Submission of 9 pharmacology/toxicology reports and 3 final clinical reports
July 29, 2005	Submission of new protocol, amendment and investigators for CA163085
July 29, 2005	Submission of BMS responses to FDA's question for proposed trade name
August 11, 2005	Submission of investigator information for CA163046, CA163048 and CA163081

September 8, 2005	Submission of protocol amendments for CA163046, CA163048 and CA163081 and investigator information for CA163085
September 12, 2005	Submission of 7 pharmacology/toxicology reports
September 26, 2005	Submission of IND annual report covering the interval of July 30, 2004 through July 29, 2005
October 10, 2005	Request for Special Protocol Assessment for prostate cancer
October 19, 2005	FDA comments on briefing document for End of Phase 2 meeting
November 4, 2005	Submission of administrative letters for CA163048 and investigator information for CA163011
November 9, 2005	Submission of 5 pharmacology/toxicology reports and 1 clinical report
November 18, 2005	FDA acknowledgement of Special Protocol Assessment request submitted on October 10, 2005
November 23, 2005	FDA's comments to Special Protocol Assessment submitted on October 10, 2005
December 2, 2005	Submission of new investigators for CA163048
January 9, 2006	Submission of request for Pre-NDA for metastatic breast cancer
January 13, 2006	Submission of request for FDA feedback on stability program
January 18, 2006	FDA confirmation of Pre-NDA meeting on March 6, 2006
January 24, 2006	Submission of 4 pharmacology/toxicology reports and 4 clinical reports
February 3, 2006	Submission of background document for Pre-NDA meeting on March 6, 2006
February 14, 2006	Submission of protocol amendment for CA163102 and investigator information for CA163046, CA163048, CA163081 and CA163085
February 17, 2006	Submission of 1 pharmacology/toxicology report and 3 clinical reports
March 2, 2006	FDA's responses to Pre-NDA meeting questions in background document
March 13, 2006	Submission of Pre-NDA meeting minutes for March 6, 2006
March 14, 2006	Submission of request for CMC Pre-NDA Meeting regarding stability data
March 23, 2006	Submission of CA163046 statistical analysis plan for FDA review
March 24, 2006	Submission of CMC information for new 10 mg delayed release capsule formulation
March 27, 2006	Submission of new protocol and investigators for CA163088
April 3, 2006	Submission of Investigator Brochure Version No. 7

April 7, 2006	Submission of imaging submission plan for FDA review
April 18, 2006	Submission of final Independent Radiology Committee Charters for CA163046 and CA163081
April 18, 2006	Submission of 18 pharmacology/toxicology reports and 5 clinical reports
April 21, 2006	Submission of background document for CMC Pre-NDA meeting
April 28, 2006	Submission of amendment to CA163080, administrative letters for CA163085 and investigator information for CA163046 and CA163048
May 4, 2006	FDA's responses to CMC Pre-NDA meeting questions in background document
May 16, 2006	Submission of new investigator information and administrative letter for CA163048, 3 pharmacology/toxicology reports and 2 clinical reports
June 15, 2006	Submission of investigator information for CA163012, CA163046 and CA163048
June 22, 2006	Submission of 2 clinical reports
July 20, 2006	Submission of Transfer of Obligations to CRO for CA163046, CA163048, CA163085, CA163088 and CA163102 and CA163081 and erratum to clinical report for CA163081
July 24, 2006	FDA meeting minutes for Pre-NDA Meeting March 6, 2006
July 26, 2006	Submission of administrative letter for CA163048, erratum to clinical study reports for CA163008, CA163009, CA163010, CA163011, CA163031, CA163036, CA163042, CA163051 and CA163080 and investigator information for CA163048
August 22, 2006	FDA's responses regarding content of NDA
August 31, 2006	Submission of cross-referencing plan for submitting IND for new oral dosage form
August 31, 2006	FDA's decision for BMS to submit NDA with data from monotherapy and combination studies
August 31, 2006	FDA's comments to BMS imaging submission on April 18, 2006
September 6, 2006	Submission of administrative letter for CA163081 and new investigators for CA163088
September 27, 2006	Submission of IND annual report covering the interval of July 30, 2005 through July 29, 2006
September 27, 2006	FDA confirms that oral IND cross-referencing plan is acceptable
September 29, 2006	Submission of BMS confirmation that NDA will be submitted with monotherapy and combination indications
October 10, 2006	Submission of 14 clinical study reports and 4 pharmacology/toxicology reports

October 31, 2006	Submission of new protocol CA163115
November 20, 2006	Submission of Proposed Pediatric Study Request
November 28, 2006	Submission of request for Pre-NDA Meeting for metastatic breast cancer
November 28, 2006	Submission of request for comments to revised imaging submission
December 14, 2006	FDA confirms Pre-NDA Meeting on February 15, 2007
December 14, 2006	FDA provides responses to imaging submission questions
December 19, 2006	Submission of new protocol and new investigators for CA163116
December 20, 2006	Submission of response to FDA comments on imaging submission
January 3, 2007	Submission of 10 pharmacology/toxicology reports and 3 clinical reports
January 11, 2007	Submission of background document for Pre-NDA Meeting on February 15, 2007
January 18, 2007	Submission of investigator information for CA163048 and CA163116
January 23, 2007	Submission of final Data Monitoring Committee Charters for CA163046 and CA163048
February 9, 2007	FDA's responses to questions in background document for Pre-NDA Meeting on February 15, 2007
February 21, 2007	FDA's response to Proposed Pediatric Study Request
February 23, 2007	NDA CMC Update fax from BMS regarding 45 mg/vial
February 23, 2007	Submission of cross-referencing of safety and information amendment submissions between IV and oral INDs
February 26, 2007	Submission of BMS minutes for Pre-NDA Meeting on February 15, 2007
February 28, 2007	Submission of 1 pharmacology/toxicology report and 5 clinical reports
March 6, 2007	Submission of Pediatric Study Request in FDA requested format
March 12, 2007	FDA accepts BMS proposal for submission of 45 mg/vial in NDA
March 13, 2007	BMS request for meeting to discuss overall survival analysis in CA163046
March 14, 2007	FDA confirms meeting on March 21, 2007 to discuss overall survival analysis for CA163046
March 15, 2007	FDA requests a meeting to discuss Pediatric Study Request on March 23, 2007
March 17, 2007	FDA sends list of questions for March 23, 2007 pediatric meeting
March 21, 2007	Submission of protocol amendment for CA163115 and investigator information for CA163115 and CA163046
March 21, 2007	FDA's responses to questions for March 21, 2007, overall survival in CA163046 meeting

March 22, 2007	Submission of BMS Pre-NDA follow-up meeting minutes on overall survival
March 29, 2007	Submission of BMS minutes of pediatric meeting on March 23, 2007
March 30, 2007	Submission of CMC information on 45 mg/vial and 23.5 mL/vial vehicle for constitution
April 2, 2007	Submission of CMC starting material information
April 3, 2007	Submission of Investigator Brochure Version No. 8
April 4, 2007	Submission of response to FDA request regarding QTc evaluation in oral program
April 5, 2007	Submission of BMS response to FDA comments on Proposed Pediatric Study Request
April 16, 2007	NDA Submission for Breast Cancer as monotherapy or in combination with capecitabine
April 18, 2007	Submission of an administrative letter for CA163048, investigator information for CA163115, CA163116 and CA163046 and change in safety personnel
April 25, 2007	FDA confirms Post-submission meeting on May 24, 2007
May 1, 2007	Submission of Imaging Submission clarification to NDA
May 16, 2007	Submission of administrative letters for CA163046, CA163048, CA163085 and CA163115 and new investigator information for CA163048
May 18, 2007	BMS sent the draft slides for the Post-Submission Meeting with FDA on May 24, 2007
June 8, 2007	Response to FDA's question regarding where the DMF references and comparative batch composition information for proposed commercial lots are located in the NDA
June 12, 2007	BMS agrees to submit pediatric studies by December 28, 2012
June 14, 2007	Submission of new investigators for CA163115 and CA163116
June 15, 2007	FDA sends NDA filing letter
June 22, 2007	FDA sends official Written Request Letter
June 25, 2007	FDA sends requests from clinical review team for CA163081
June 27, 2007	Submission of response to clinical request for CA163081 to NDA
June 27, 2007	FDA sends Day 74 potential review issues letter with comments to package insert
July 3, 2007	Submission of plan for oral and IV IND Annual Reports
July 6, 2007	Submission of BMS acknowledgement of FDA's comments to proposed package insert
July 10, 2007	FDA's fax with requests from Department of Scientific Investigation regarding clinical site inspections

July 12, 2007	Submission of investigator information for CA163046, CA163048 and CA163085
July 12, 2007	Submission of Data Monitoring Committee overall survival analysis information for CA163046
July 12, 2007	FDA sends requests from statistical review team for NDA
July 13, 2007	Submission of response to FDA requests from statistical review team for NDA
July 17, 2007	Submission of addendum to CA163081 final study report
July 24, 2007	Submission of response to FDA request for xenograft data
July 25, 2007	Submission of information requested by Division of Scientific Investigations for clinical site inspections
July 27, 2007	Submission of new protocol CA163100, protocol amendment for CA163116 and investigator information for CA163046, CA163081, CA163100 and CA163116
August 7, 2007	Submission of 120 day safety update for NDA
August 10, 2007	FDA sends CMC requests
August 13, 2007	FDA confirms that IV and oral IND Annual Reports can be synchronized
August 17, 2007	FDA sends statistical comments to CA163115
August 22, 2007	Submission of Transfer of Obligations for CA163048, CA163085, CA163088, CA163100, CA163102, CA163115, CA163116 to Accenture Services and new investigators for CA163115 and CA163116
August 29, 2007	FDA sends CMC requests for NDA
August 30, 2007	Submission of response to CMC requests on August 10, 2007
September 4, 2007	Submission of response to FDA statistical comments to CA163115
September 4, 2007	FDA sends clinical request for NDA
September 4, 2007	Submission of response to CMC requests on August 29, 2007
September 5, 2007	FDA sends microbiology requests for CMC section of NDA
September 6, 2007	Submission of response to clinical request on September 4, 2007
September 6, 2007	FDA sends request for aseptic process validation data
September 6, 2007	FDA notifies BMS of sponsor-monitor inspection on September 11, 2007
September 7, 2007	Confirmation letter for inspection of Dr. Li's site in the Philippines
September 10, 2007	FDA sends CMC requests for NDA
September 11, 2007	Submission of response to CMC requests on September 5, 2007
September 11, 2007	FDA sends clinical comments for NDA
September 12, 2007	FDA instructs BMS to disregard clinical comments on September 11, 2007

September 13, 2007	FDA sends statistical requests for NDA
September 14, 2007	Submission of CMC response to requests on August 29, and September 7, 2007
September 14, 2007	Submission of CMC responses to microbiology requests on September 5, 2007
September 18, 2007	Submission of response to statistical comments to NDA on September 13, 2007
September 19, 2007	FDA sends CMC requests for NDA regarding capping pressure
September 20, 2007	Submission of response to CMC requests regarding capping pressure on September 19, 2007
September 21, 2007	Submission of response to microbiology comments on CMC section on September 5, 2007, and response for aseptic process validation data
September 24, 2007	Submission of response to statistical comments on September 13, 2007
September 24, 2007	FDA sends request regarding adverse events in CA163081
September 25, 2007	Submission of IND annual report covering the interval of July 30, 2006 through July 29, 2007
September 26, 2007	FDA confirms that manufacturing inspections are not considered pre-approval inspections
September 27, 2007	BMS provides Module 2 and 3 CMC information as background for manufacturing inspections
September 28, 2007	FDA sends revisions to proposed labeling
October 2, 2007	FDA requests proposed dates for BMS commitment to fulfill Post Marketing Study Commitments
October 2, 2007	Submission of response to statistical comments
October 2, 2007	FDA sends statistical requests for NDA
October 3, 2007	Submission of response to statistical comments on October 2, 2007
October 3, 2007	Submission of revised labeling based on FDA revisions on September 28, 2007
October 4, 2007	Submission of response to FDA request regarding Post Marketing Study Commitments on October 2, 2007
October 4, 2007	FDA requests a high level summary of BMS' revisions to label and a tracked changes document in Word
October 4, 2007	Submission of new investigators for CA163116 and Transfer of Obligations to Accenture Services for CA163046
October 5, 2007	Submission of response to FDA labeling request on October 4, 2007
October 5, 2007	FDA sends revisions to patient information
October 5, 2007	Submission of response to Post Marketing Study Commitments
October 9, 2007	FDA requests that BMS review proposed Post Marketing Commitments

October 10, 2007	BMS response regarding Post Marketing Commitments
October 10, 2007	FDA comments to response for Post Marketing Commitments
October 11, 2007	FDA provides comments from DMETs and CMC recommendations
October 11, 2007	FDA sends label change to pregnancy section
October 12, 2007	Submission of revised labeling and Post Marketing Commitments based upon FDA revisions on October 5, 10 and 11, 2007
October 12, 2007	Submission of response to FDA regarding CMC comments
October 12, 2007	FDA sends revised labeling
October 12, 2007	FDA sends draft Ixempra burst for BMS comment
October 12, 2007	FDA sends statistical comments
October 15, 2007	Submission of revised labeling in response to FDA revision on October 12, 2007, along with revised 45 mg carton label
October 15, 2007	Submission of response to FDA request on October 15, 2007 regarding Post Marketing Commitments
October 15, 2007	BMS sends comments to FDA's draft Ixempra burst
October 16, 2007	FDA sends approval letter for NDA

(12) In the opinion of applicant, U.S. Patent 6,605,599B1 is eligible for the extension under 35 U.S.C. §156. Applicant believes that the extension should be for 854 days so that the expiration date for U.S. Patent 6,605,599 B1 will be September 27, 2020. The term of the extension was calculated as follows:

Period of Extension = ½ (Testing phase) + Approval phase
= ½ (1342) + 184
= 855 days

Testing phase:

Since the regulatory review period began in June 1999, before the patent issued on August 12, 2003, only that portion of the regulatory review period occurring after the date the patent issued has been considered:

From and including: Wednesday, August 13, 2003 (day **after** patent grant)
To, but **not** including April 16, 2007 = 1342 days

Approval Phase:

From and including: Monday, April 16, 2007 (day NDA was filed)
To, **and** including October 16, 2007 (day NDA was approved) = 184 days

Neither the limitations of 35 U.S.C. § 156(g)(6), nor 35 U.S.C. § 156(c)(3), operate to reduce the period of extension determined above, as the total exclusivity period is less than 14 years (approximately 12.9 years), and the total extension period is less than 5 years (e.g., is approximately 2.3 years).

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extent sought in accordance with 37 C.F.R. §1.765.

(14) Authorization is given to charge the fee of $1,120.00 for receiving and acting upon the application for extension to the Deposit Account No. 19-3880 of the undersigned. Additionally, the Commissioner is authorized to charge any additional fee that may

be required to process this extension request to the aforementioned Deposit Account.

(15) Please direct any inquiries and correspondence relating to the application for patent term extension to:

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Date:November 15, 2007

US006605599B1

(12) **United States Patent**
Vite et al.

(10) **Patent No.: US 6,605,599 B1**
(45) **Date of Patent: Aug. 12, 2003**

(54) **EPOTHILONE DERIVATIVES**

(75) Inventors: **Gregory D. Vite**, Titusville, NJ (US); **Soong-Hoon Kim**, Lawrenceville, NJ (US); **Robert M. Borzilleri**, Lawrenceville, NJ (US); **James A. Johnson**, Lawrenceville, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/084,542**

(22) Filed: **May 26, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/067,524, filed on Dec. 4, 1997, and provisional application No. 60/051,951, filed on Jul. 8, 1997.

(51) **Int. Cl.**[7] **C07D 493/04**; C07D 417/06; C07D 277/20; C07D 277/26; A61K 31/425

(52) **U.S. Cl.** **514/63**; 514/183; 514/365; 514/366; 514/450; 540/452; 540/462; 540/463; 540/468; 548/202; 548/203; 548/204; 549/346; 549/355

(58) **Field of Search** 514/63, 183, 365, 514/450; 540/452, 462, 463, 468; 548/203, 204; 549/346, 355

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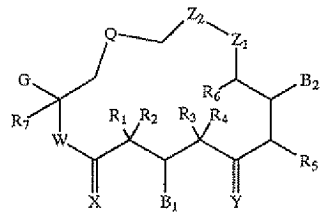
Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Rena Patel

(57) **ABSTRACT**

The present invention relates to epothilone derivatives, having the following formula



in which the variables G, W, Q, X, Y, B_1, B_2, Z_1, Z_2, and R_1–R_7 are as defined herein, methods for the preparation of the derivatives and intermediates thereof.

62 Claims, No Drawings

EPOTHILONE DERIVATIVES

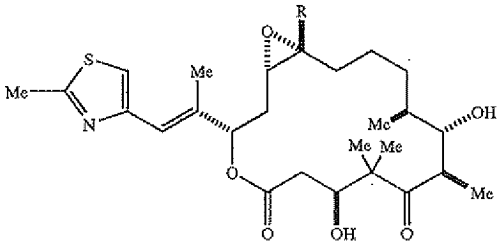
FIELD OF THE INVENTION

This application claims benefit to U.S. Provisional Application Serial No. 60/051,951, filed Jul. 8, 1997 which claims benefit to U.S. Provisional Application Serial No. 60/067,524, filed Dec. 4, 1997.

The present invention relates to epothilone derivatives, methods for the preparation of the derivatives and intermediates therefor.

BACKGROUND OF THE INVENTION

Epothilones are macrolide compounds which find utility in the pharmaceutical field. For example, Epothilones A and B having the structures:



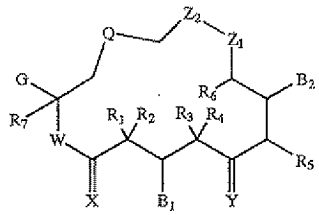
I Epothilone A R = H
II Epothilone B R = Me

have been found to exert microtubule-stabilizing effects similar to TAXOL and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease, see Angew. Chem. Int. Ed. Engl., 1996, 35, No. 13/14.

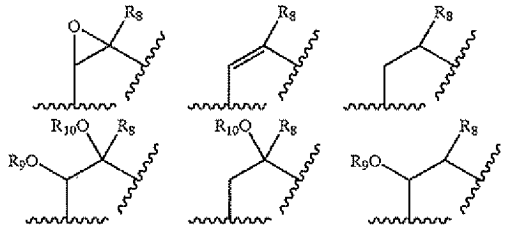
SUMMARY OF THE INVENTION

The present invention relates to compounds of the formula

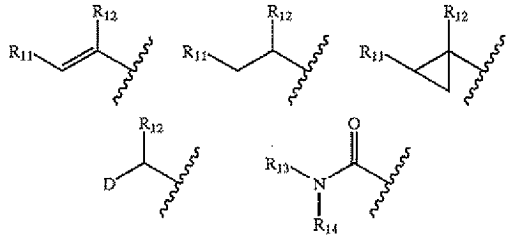
V



Q is selected from the group consisting of



G is selected from the group consisting of alkyl, substituted alkyl, substituted or unsubstituted aryl, heterocyclo,



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; or CHR_{22}; OR_{17} OR_{17} can be a cyclic ketal;

Z_1, and Z_2 are selected from the group consisting of CH_2, O, NR_{23}, S, or SO_2, wherein only one of Z_1 and Z_2 can be a heteroatom;

B_1 and B_2 are selected from the group consisting of OR_{24}, or $OCOR_{25}$, or $O_2CNR_{26}R_{27}$; when B_1 is OH and Y is OH, H they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$ or saturated heterocycle;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26}, and R_{27} are selected from the group H, alkyl, substituted alkyl, or aryl and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl; R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25}, and R_{31} are selected from the group H, alkyl, or substituted alkyl;

R_8, R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, R_{33}, and R_{30} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, or heterocyclo;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C{=}O$, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl;

and any salts, solvates or hydrates thereof.

Proviso

The present invention does not include compounds of formula V wherein

W and X are both O; and

R_1, R_2, R_7, are H; and

R_3, R_4, R_6, are methyl; and

R_8, is H or methyl; and

Z_1, and Z_2, are CH_2; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

Q is as defined above.

DETAILED DESCRIPTION OF THE INVENTION

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyoxy, heterocylooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g. $CONH_2$), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocyclooxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "cycloalkyl" refers to optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocycio" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b] pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclos, such as, epoxides and aziridines.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The compounds of formula V may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be obtained, for example, by exchanging the carboxylic acid protons, if they contain a carboxylic acid, in compounds of formula V with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by evaporation. Other salts can be formed as known to those skilled in the art.

The compounds for formula V form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, hydroxyethanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts are formed by reacting a compound of formula V in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

In addition, zwitterions ("inner salts") are formed.

Compounds of the formula V may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound for formula V) is a prodrug within the scope and spirit of the invention.

For example compounds of the formula V may form a carboxylate ester moiety. The carboxylate esters are conve-

niently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s).

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs,* edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology,* Vol.42, p.309–396, edited by K. Widder, et al. (Acamedic Press, 1985);

b) *A Textbook of Drug Design and Development,* edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113–191 (1991);

c) H. Bundgaard, *Advanced Drug Delivery Reviews,* 8, 1–38 (1992);

d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences,* 77, 285 (1988); and

e) N. Kakeya, et al., *Chem Phar Bull,* 32, 692 (1984).

It should further be understood that solvates (e.g., hydrates) of the compounds of formula V are also within the scope of the present invention. Methods of solvation are generally known in the art.

Use and Utility

The compounds of formula V are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers or other abnormal proliferative diseases, including (but not limited to) the following;

carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;

hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;

hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;

tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and

other tumors including melanoma, xenoderma, pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

Compounds of formula V may also inhibit tumor angiogenesis, thereby affecting abnormal cellular proliferation. Such anti-angiogenesis properties of the compounds of formula V may also be useful in the treatment of certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Compounds of formula V may induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of formula V, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostrate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including but not limited to systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula V can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, e.g. S phase, than the present compounds of formula V which exert their effects at the G_2-M phase.

e.g.

Thymidilate Synthase Inhibitors,

DNA Cross Linking Agents

Topoisomerase I and II Inhibitors

DNA Alkylating Agents

Ribonucleoside Reductase Inhibitors

Cytotoxic Factors e.g. TNF-alpha or

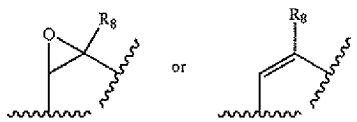
Growth factor inhibitors e.g. HER 2 receptor MAB's

The present compounds may exist as multiple optical, geometric, and stereoisomers. Included within the present invention are all such isomers and mixtures thereof.

The compounds of this invention can be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds are administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Preferred Compounds

Especially preferred compounds of formula V are those wherein



X is O

Y is O

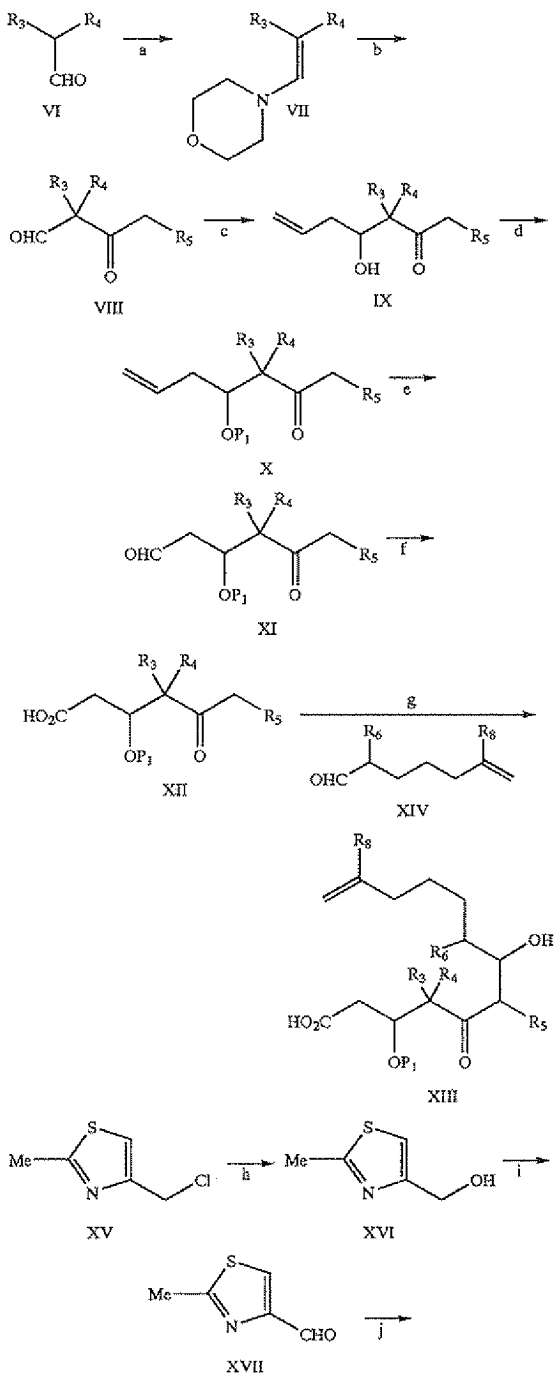
Z_1 and Z_2 are CH_2 and

W is NR_{15}.

Method of Preparation

Compounds of formula V are prepared by the following schemes.

Scheme 1



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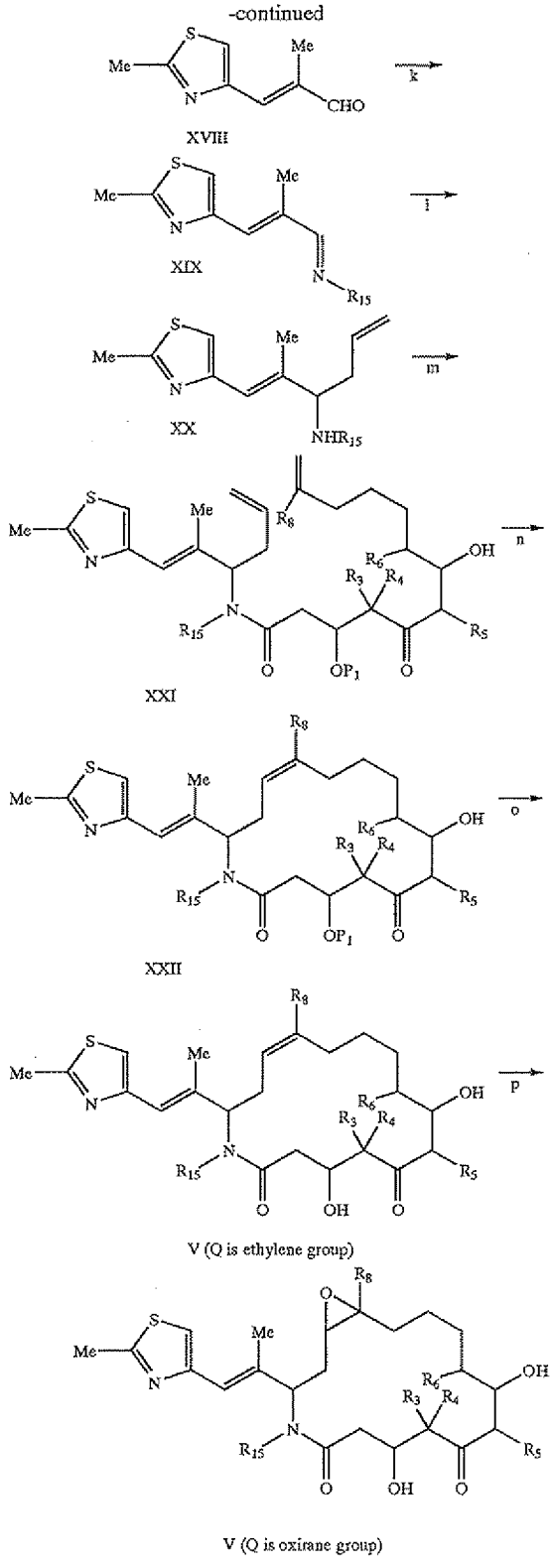
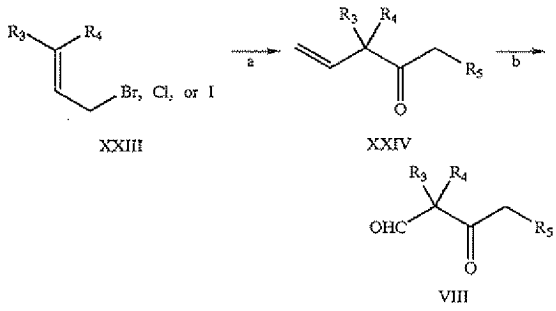


wherein R_3, R_4, R_5, R_6, R_8 and R_{15} are as above and P_1 is an oxygen protecting group.

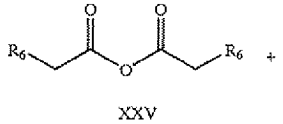
Compounds of formula V where W is NR_{15} and X is O can be prepared as outlined in Scheme 1. A compound of formula XII, where P_1 is an oxygen protecting group such as t-butyldimethylsilyl, can be prepared from a compound of formula VI by known methods (i.e., Nicolaou, K. C., et al., *Angew. Chem. Int. Ed. Engl.*, (1997) 36, 166–168). Aldol reaction of a compound of formula XII and a compound of formula XIV provides a compound of formula XIII. The compound of formula XIV can be prepared by known methods (i.e., Schinzer, D., et al., *Eur. Chem. Chron.*, (1996) 1, 7–10). An aldehyde of formula XVIII can be prepared from a compound of formula XV as shown in Scheme 1 or by using known methods (i.e., Taylor, R. E., et al., *Tetrahedron Lett.*, (1997), 38, 2061–2064). A compound of formula XIX can be prepared from a compound XVIII by treatment with an amine using dehydrating conditions such as catalytic p-toluenesulfonic acid and azeotropic removal of water. A compound of formula XX can be prepared from a compound of formula XIX by treatment with an allylating reagent such as allylmagnesium bromide. A compound of formula XXI can be prepared from compounds of formulas XIII and XX, by standard amide bond coupling agents (i.e., DCC, BOP, EDC/HOBT, PyBrOP). A compound of formula XXII can be prepared from a compound of formula XXI by ring-closing metathesis using either the Grubbs ($RuCl_2(=CHPh)(PCY_3)_2$; see Grubbs, R. H., et al., Angew. Chem. Int. Ed. Engl.; (1995) 34, 2039) or Schrock catalysts (See Schrock, R. R., et al., *J. Am. Chem. Soc.*, (1990) 112, 3875). Deprotection of a compound of formula XXI using, for example when P_1 is a t-butyldimethylsily group, hydrogen fluoride in acetronitrile or tetra-n-butyl ammonium fluoride in THF provides a compound of formula V where Q is an ethylene group, W is NR_{15}, X is O, an R_3, R_4, R_5, R_6 are defined as described above. Regioselective epoxidation of a compound of formula V where Q is an ethylene group using dimethyldioxirane provides a compound of formula V where Q is an oxirane group, W is NR_{15}, X is O, and R_3, R_4, R_5, R_{15} are defined as described above.

Scheme 2



Alternatively, a compound of formula VIII can be prepared by reaction of a compound of formula XXIII with magnesium and an acid chloride (R_5CH_2COCl) to give a compound of formula XXIV (See for example: Heathcock, C.; et. al., *J.Org. Chem.*, 1990, 55, 1114–1117), followed by ozononolysis to give a compound of formula VIII as shown in Scheme 2.

Scheme 3



XXV

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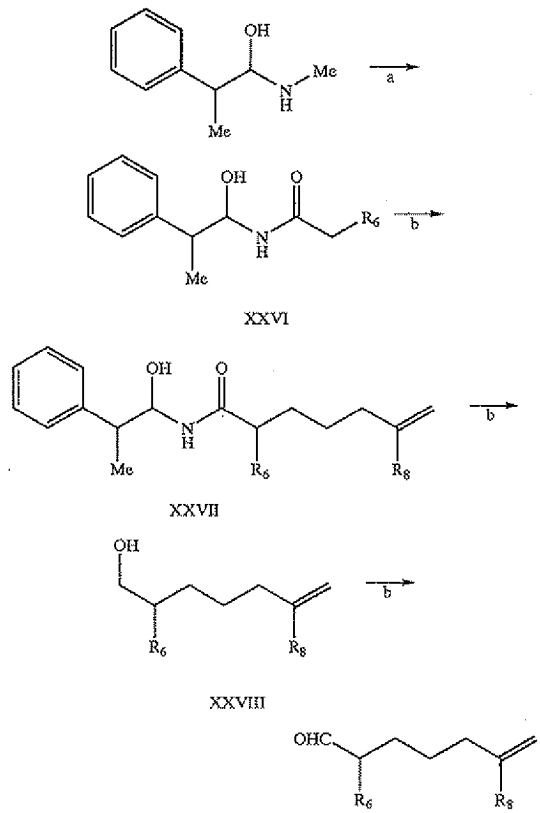
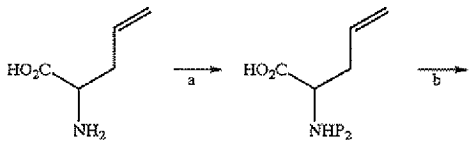


Alternatively, a compound of formula XIV can be prepared as shown in Scheme 3. Reaction of a compound of formula XXV and pseudoephedrine provides a compound of formula XXVI. A compound of formula XXVII can be prepared from a compound of formula XXVI by alkylation with a pentenyl halide such as 5-bromopentene according to the method of Meyers (i.e., Meyers, A.; et. al., *J. Am. Chem. Soc.*, 1994, 116, 9361–9362). A compound of formula XXVIII can be prepared from a compound of formula XXVII with a reducing agent such as lithium pyrrolidinyl borohydride. Oxidation of a compound of formula XXVIII, using for example pyridinium chlorochromate, provides a compound of formula XIV. Direct conversion of a compound of formula XXVII to a compound of formula XIV can be accomplished with a reducing agent such as lithium triethoxy-aluminum hydride.

Scheme 4



XXIX

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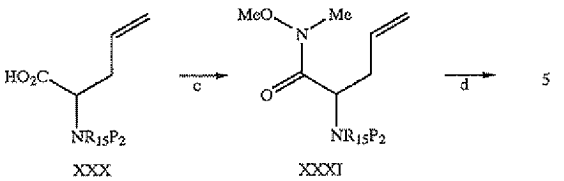
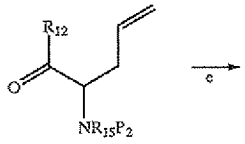
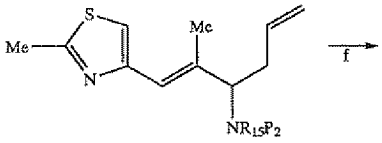


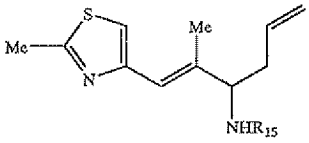
XXX XXXI



XXXII



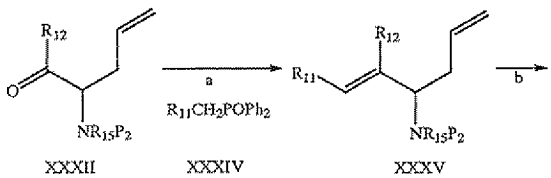
XXXIII



XX

Alternatively, a compound of formula XX can be prepared from allylglycine as shown in Scheme 4. Allylglycine can be N-protected using methods known in the art to give a compound of formula XXIX, where P_2 is a suitable N-protecting group such as t-butyloxycarbonyl. Optionally, where R_{29} is not hydrogen, a compound of formula XXX can be prepared from a compound of formula XXIX by alkylation with an alkyl halide in the presence of a base such as sodium hydride. A compound of formula XXI can be prepared from a compound of formula XXX using N,O-dimethylhydroxylamine and standard coupling agents such as EDCI and HOBT. A compound of formula XXXII can be prepared from a hydroxamate XXXI by treatment with an organometallic reagent such as an alkyl or arylmagnesium halide. Wittig olefination of a compound of formula XXII provides a compound of formula XXXIII (the Wittig reagent is prepared as reported: Danishefsky, S. E.; et. al., *J. Org. Chem.*, 1996, 61, 7998–7999). N-Deprotection of a compound of formula XXIII using methods known in the art provides a compound of formula XX.

Scheme 5



XXXII XXXIV XXXV

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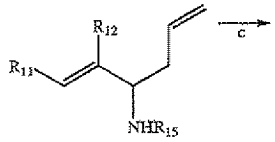
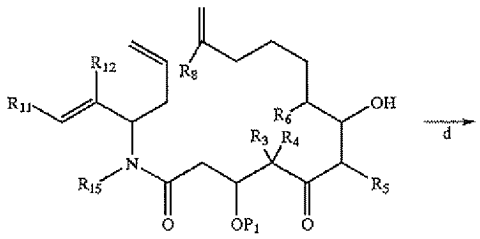
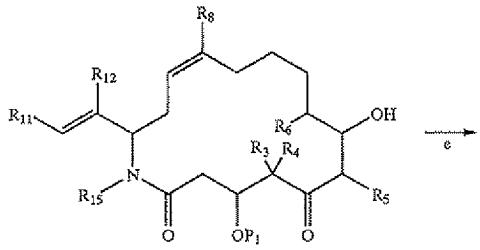


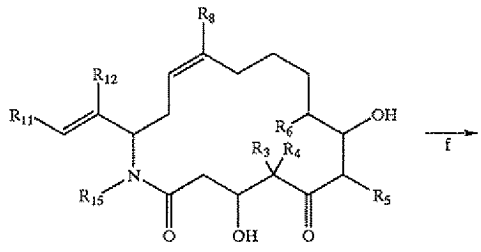
XXXVI



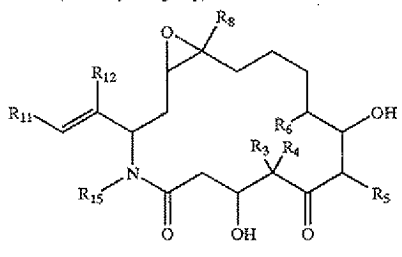
XXXVII



XXXVIII



V(Q is ethylene group)

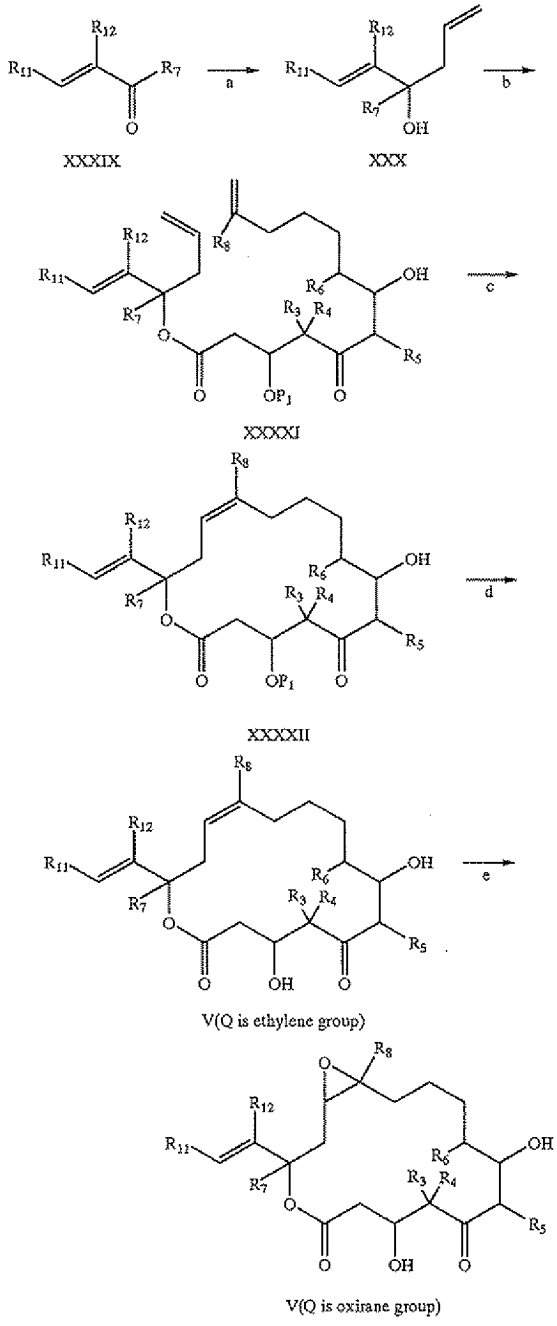


V(Q is oxirane group)

A compound of formula V where W is NR_{15}, X is oxygen, and G is a 1,2-disubstituted olefin can be prepared as shown in Scheme 5. A compound of formula XXXV can be prepared by Wittig olefination of a compound of formula XXXII. A compound of formula XXXIV can be prepared by methods known in the art. A compound of formula XXXVI can be prepared by N-deprotection of a compound of formula XXXV using methods known in the art. A compound of formula XXXVI can be prepared by coupling reaction of a compound of formula XXXVI and a compound of formula XIII using standard coupling agents such as EDCI and HOBT. A compound of formula XXXVIII can be

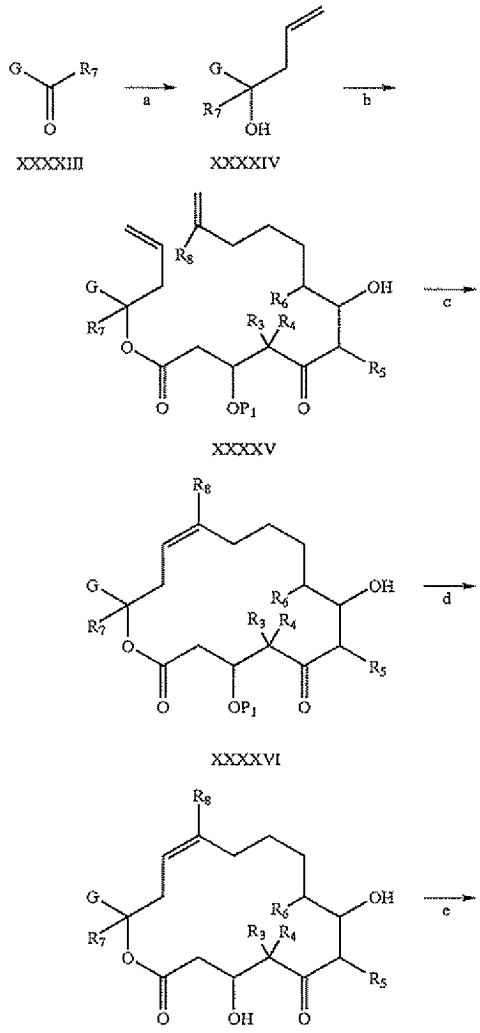
prepared from a compound of formula XXXVIII by methods described in Scheme 1 for the preparation of a compound of formula XXII. Using methods described in Scheme 1 (steps o and p), a compound of formula XXXVIII can be converted to compounds of formula V where W is NR_{15}, X is oxygen, and G is a 1,2-disubstituted olefin.

Scheme 6



A compound of formula V where both W and X are oxygen, and G is a 1,2-disubstituted olefin can be prepared as shown in Scheme 6. A compound of formula XXXX can be prepared from a compound of formula XXXIX by treatment with an allylating agent such as allylmagnesium bromide. Enantiomerically pure XXXX can be prepared by employing chiral reagents (see, for example: Taylor, R. E.; et. al., *Tetrahedron Lett.*, 1997, 38, 2061–2064; Nicolaou, K. C.; et. al., *Angew. Chem. Int. Ed. Engl.*, 1997, 36, 166–168, Keck, G., et. al., *J. Am. Chem. Soc.*, 1993, 115, 8467). A compound of formula XXXXI can be prepared from compounds of formula XXXX and XIII by using standard esterification methods such as DCC and DMAP. A compound of formula XXXXII can be prepared from a compound of formula XXXXI via ring-closing olefin metathesis as described in Scheme 1 for the preparation of a compound of formula XXII. Compounds of formula V where both W and X are oxygen, and G is a 1,2-disubstituted olefin can be prepared from a compound of formula XXXXII by deprotection (where Q is an ethylene group) and, if desired, epoxidation (where Q is an oxirane group) as described above.

Scheme 7



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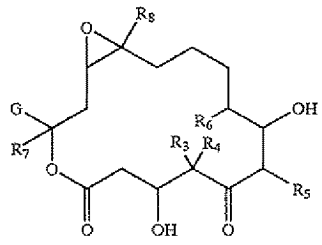

V(Q is oxirane group)

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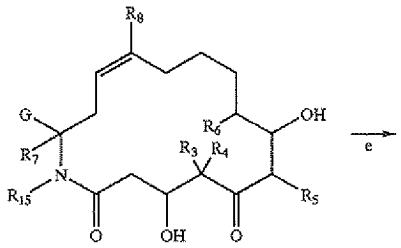
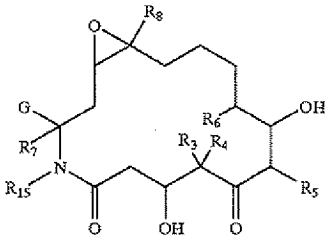


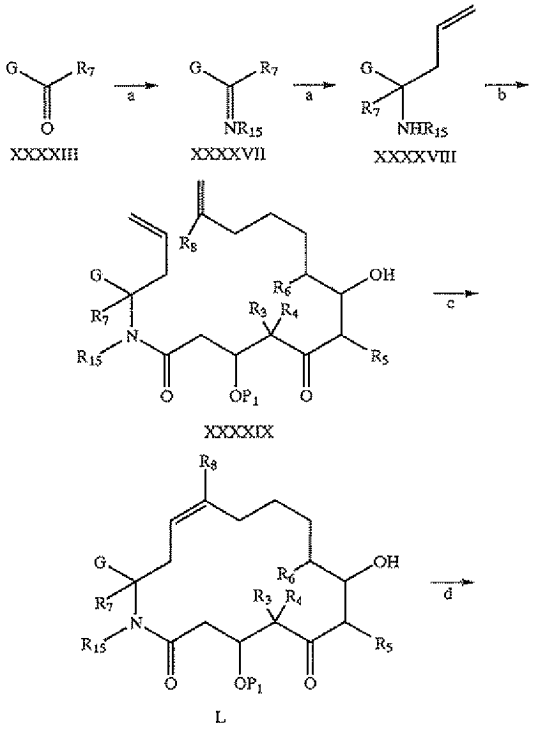
V(Q is ethylene group)



V(Q is oxirane group)

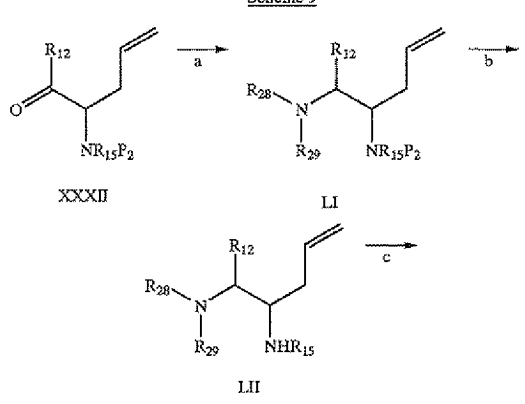
A compound of formula V where both W and X are oxygen, and G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl can be prepared as shown in Scheme 7. A compound of formula XXXXIV can be prepared by allylation of a compound of formula XXXXIII, where G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl, by reaction with an allylating reagent such as allyl magnesium bromide. A compound of formula XXXXV can be prepared from a compound of formula XXXXIV via esterification with a compound of formula XIII using, for example, DCC and DMAP. A compound of formula XXXXVI can be prepared from a compound of formula XXXXV by ring-closing metathesis as described above. Following the methods outlined above for Scheme 1, a compound of formula XXXXVI can be converted to compounds of formula V by deprotection and subsequent epoxidation.

Scheme 8



A compound of formula V where W is NR_{15}, X is oxygen, and G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl can be prepared as shown in Scheme 8. A compound of formula XXXXVII can be prepared by reaction of a compound of formula XXXXIII, where G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl, and an amine under dehydrating conditions. A compound of formula XXXXVIII can be prepared from a compound of formula XXXXVII by treatment with an allylating agent such as allylmagnesium bromide. A compound of formula XXXXIX can be prepared from a compound of formula XXXXVIII and a compound of formula XIII by standard amide bond coupling techniques using, for example, EDCI and HOBT. A compound of formula L can be prepared from a compound of formula XXXXIX by ring-closing metathesis as described above. Following the methods outlined above for Scheme 1, a compound of formula L can be converted to compounds of formulas V by deprotection and subsequent epoxidation.

Scheme 9



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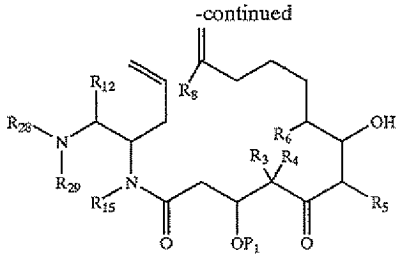
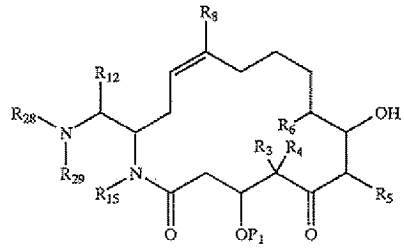
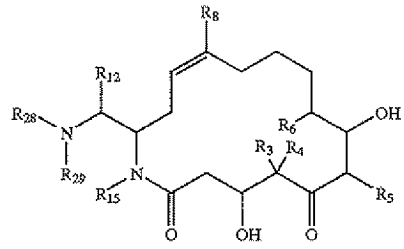
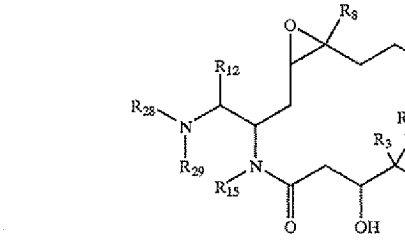




LIII



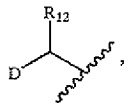
LIV



V

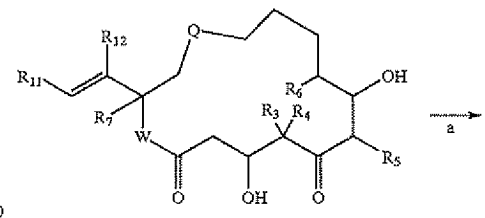
V

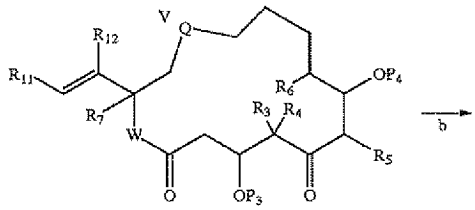
A compound of formula V where X is oxygen, W is NR_{15}, and G is

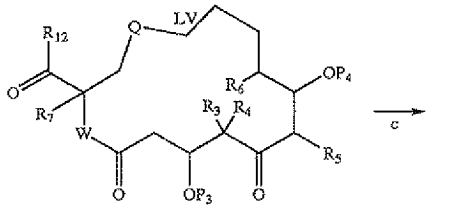


and D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$, and saturated heterocycle (i.e., piperidinyl, morpholinyl, piperazinyl, etc.) can be prepared as shown in Scheme 9. A compound of formula LI can be prepared from a compound of formula XXXII by reductive amination using a primary or secondary amine and a reducing agent such as sodium triacetoxyborohydride. Compounds of formula LIII, LIV, and V can then be prepared following methods described above in Scheme 1.

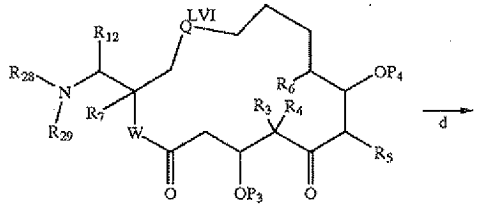
Scheme 10



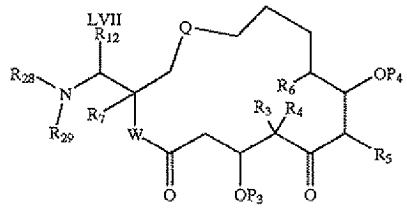




LV



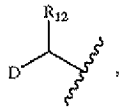
LVI



LVII

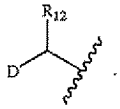
V

Alternatively, a compound of formula V where X is oxygen, W is oxygen or NR_{15} or oxygen, and G is

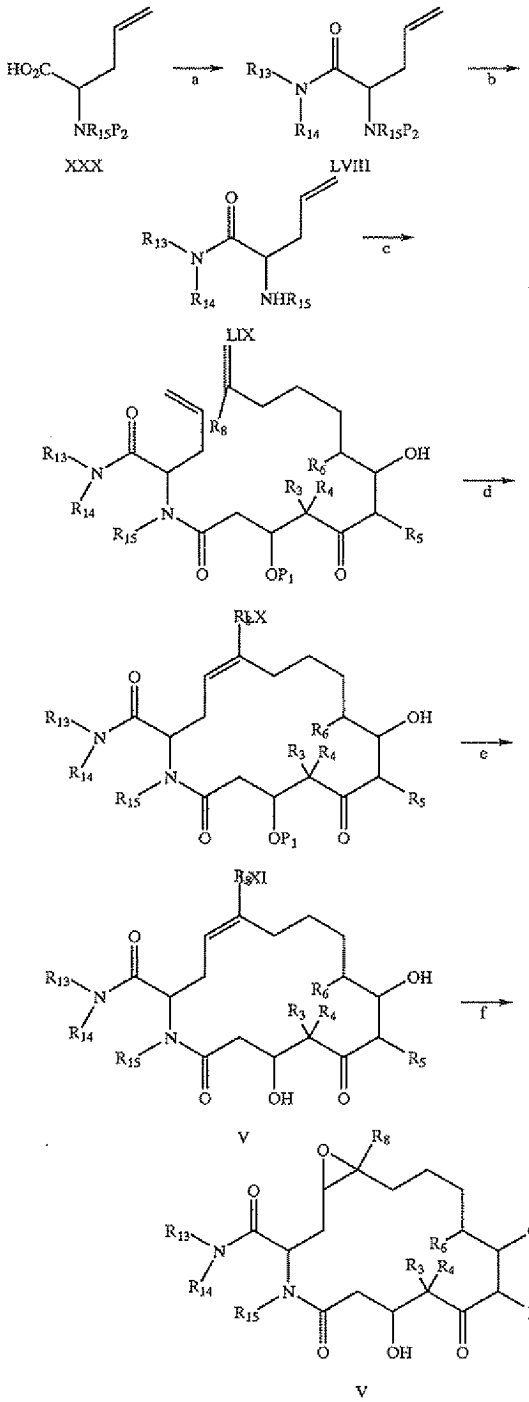


and D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$, and saturated heterocycle (i.e., piperidinyl, morpholinyl, piperazinyl, etc.) can be prepared from a compound of formula V as shown in Scheme 10. A compound of formula V can be converted to a compound of formula LV by protection of the hydroxyl groups with suitable protecting groups such as t-butyldimethylsilyl. A compound of formula LVI can be prepared from a compound of formula LV by ozonolysis. Treatment of a compound of formula LVI with an amine and a reducing agent such as sodium triacetoxyboro-hydride provides a compound of formula LVII. Removal of the protecting groups from a compound of formula LVII, with for example hydro-

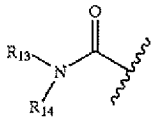
gen fluoride, provides a compound of formula V where X is oxygen, W is NR_{15} or oxygen, and G is



Scheme 11

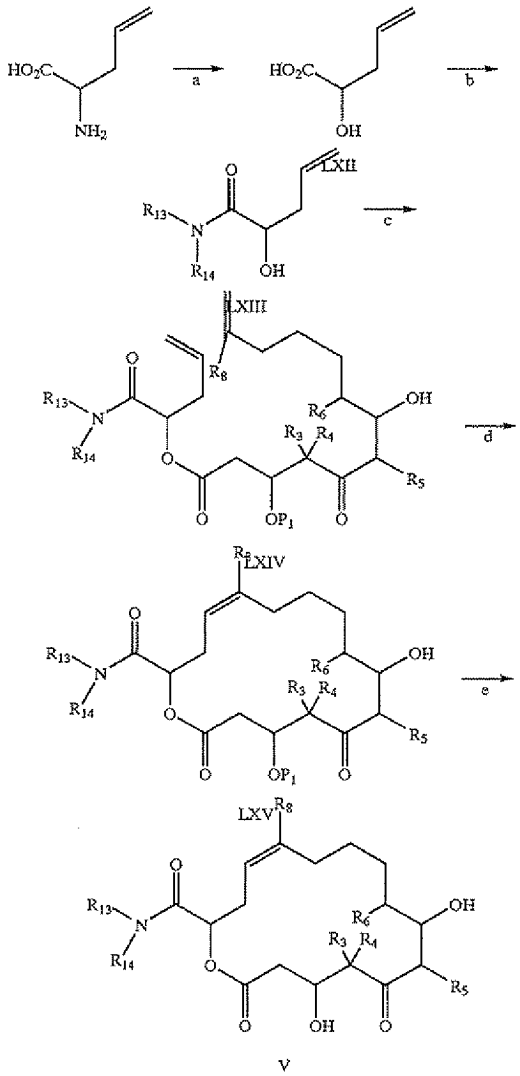


A compound of formula V where W is NR_{15}, X is oxygen, and G is

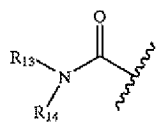


can be prepared as outline d in Scheme 11. A compound of formula LVIII can be prepared from a compound of formula XXX by treatment with an amine and standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LX can be prepared from a compound of formula LVIII by N-deprotection, using for example trifluoroacetic acid when P_2 is a t-butyloxycarbonyl group, followed by coupling of compounds of formula LIX and XIII using standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LXI can be prepared from a compound of formula LX by ring-closing metathesis. A compound of formula V can be prepared from a compound of formula LXI following methods described in Scheme 1.

Scheme 12



A compound of formula V where W is oxygen, X is oxygen, and G



can be prepared as outlined in Scheme 12. A compound of formula LXII can be prepared from allylglycine by treatment with nitrous acid. A compound of formula LXIII can be prepared from a compound of formula LXII by treatment with an amine and standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LXIV can be prepared from compounds of formula LXIII and XIII using standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LXV can be prepared from a compound of formula LXIV by ring-closing metathesis. A compound of formula V can be prepared from a compound of formula LXV following methods described in Scheme 1.

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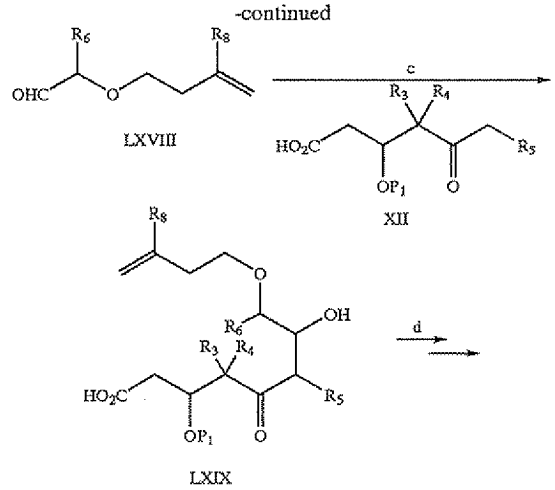
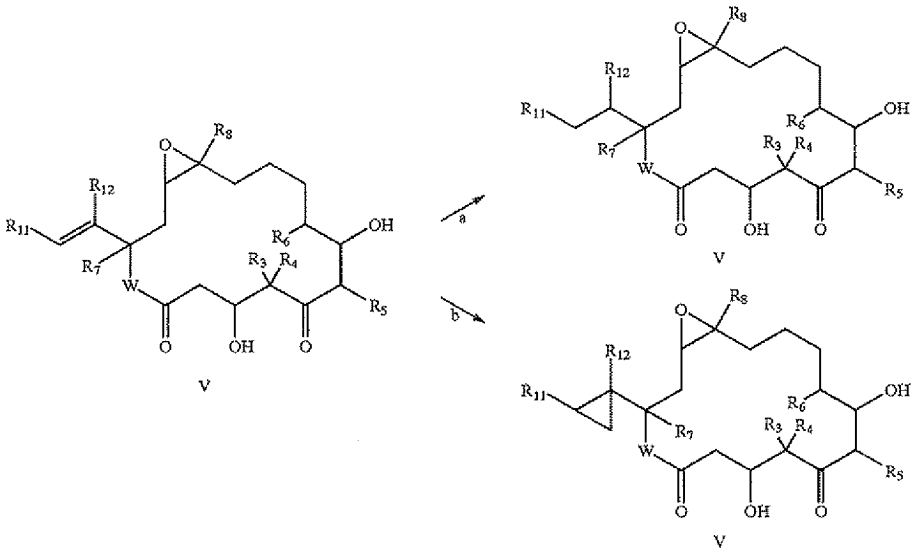


LXVIII

XII

LXIX

Scheme 13

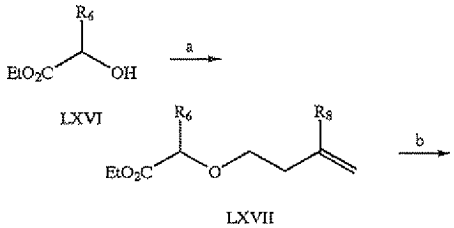


V

V

Compounds of formula V where G is a 1,2-disubstituted ethyl group can be prepared from a compound of formula V where G is a 1,2-disubstituted ethylene group by hydrogenation with a catalyst such as palladium on carbon, as shown in Scheme 13. Furthermore, compounds of formula V where G is a 1,2-disubstituted cyclopropyl group can be prepared from a compound of formula V where G is a 1,2-disubstituted ethylene group by cyclopropanation with diiodomethane and zinc-copper couple, as shown in Scheme 4.

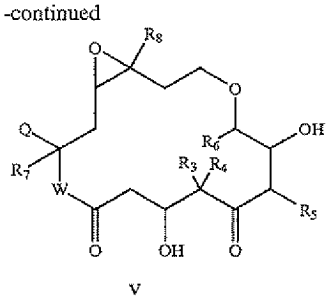
Scheme 14



LXVI

LXVII

-continued

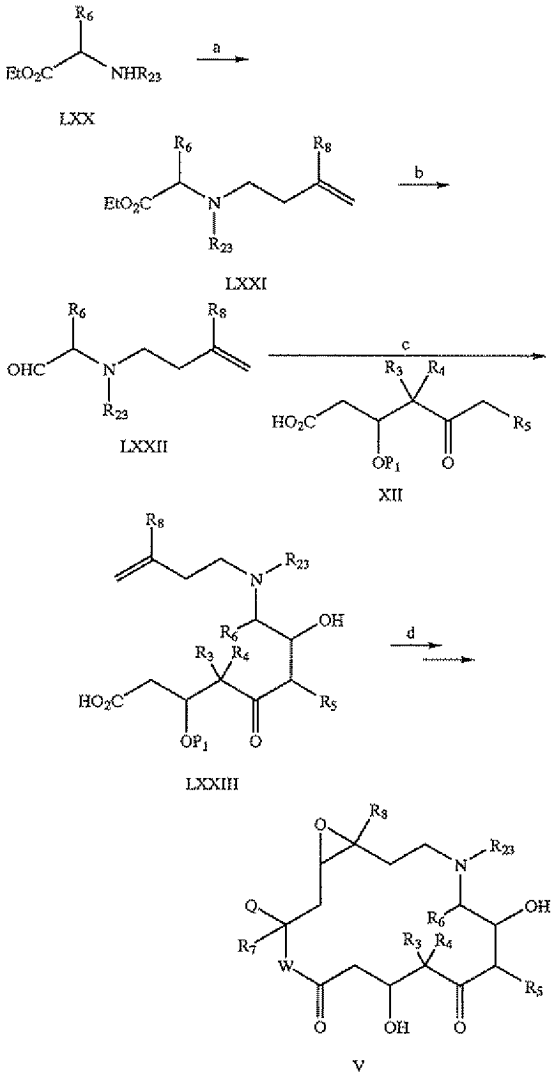


V

A compound of formula V where Z_1 is oxygen can be prepared as shown in Scheme 14. A compound of formula LXVII can be prepared from a alpha-hydroxy ester LXVI and a 3-buten-1-yl-trifluoromethanesulfonate (or with an 3-butenyl bromide and silver triflate). A compound of formula LXVII can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXVIII. Alternatively, a compound of formula LXVIII can be obtained from a compound of formula LXVII by a two step procedure involving reduction with lithium

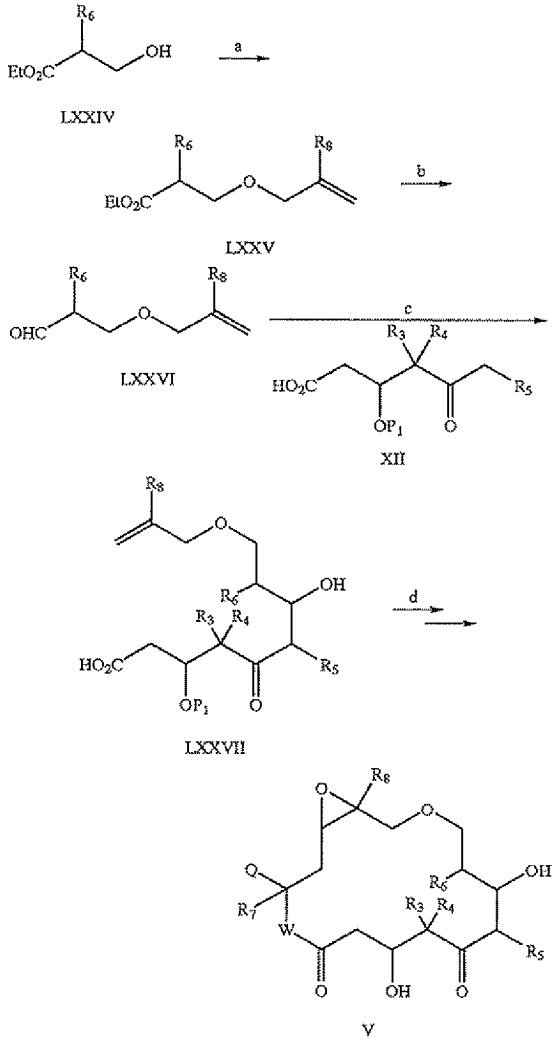
borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXVIII can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXIX. Further elaboration of LXIX as described above provides a compound of formula V where Z_1 is oxygen.

Scheme 15



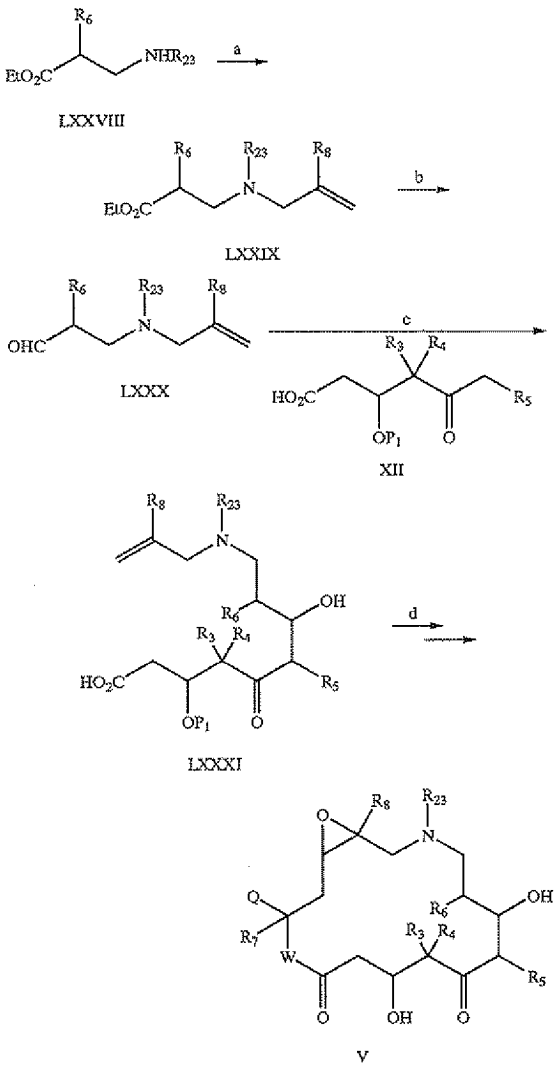
Similarly, a compound of formula V where Z_1 is NR_{23} can be prepared as shown in Scheme 15. A compound of formula LXXI can be prepared from a alpha-amino ester LXX and a 3-buten-1-yl-bromide. A compound of formula LXXI can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXII. Alternatively, a compound of formula LXXII can be obtained from a compound of formula LXXI by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXII can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXIII. Further elaboration of LXXIII as described above provides a compound of formula V where Z_1 is NR_{23}.

Scheme 16

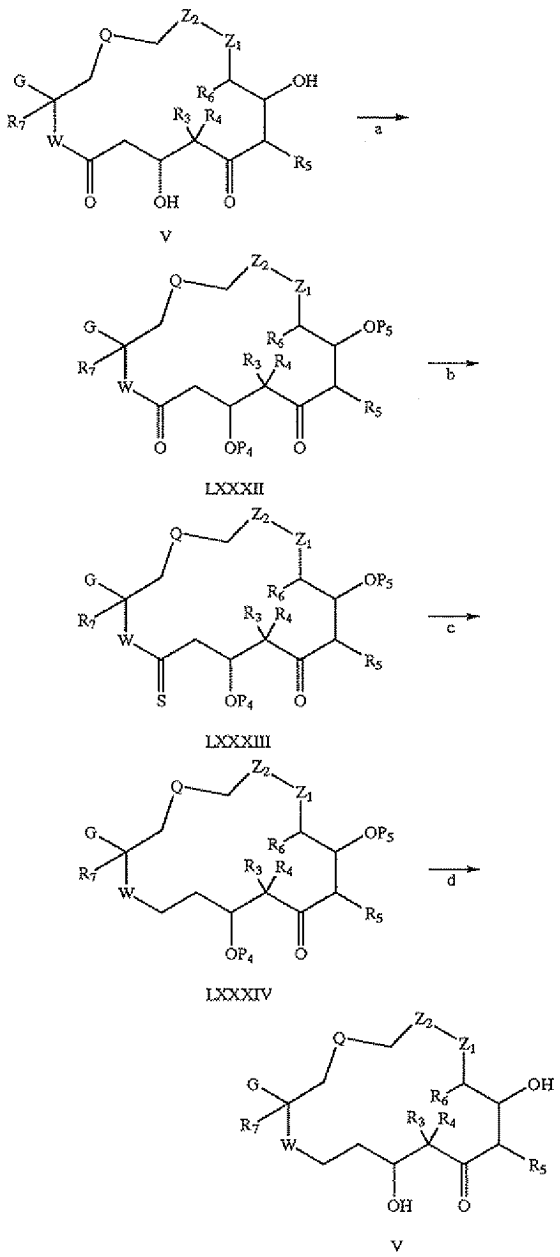


A compound of formula V where Z_2 is oxygen can be prepared as shown in Scheme 16. A compound of formula LXXV can be prepared from a beta-hydroxy ester LXXIV and an allylating agent such as allylbromide (or an allyl bromide and silver triflate). A compound of formula LXXV can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXVI. Alternatively, a compound of formula LXXVI can be obtained from a compound of formula LXXV by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXVI can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXVII. Further elaboration of LXXVII as described above provides a compound of formula V where Z_2 is oxygen.

Scheme 17



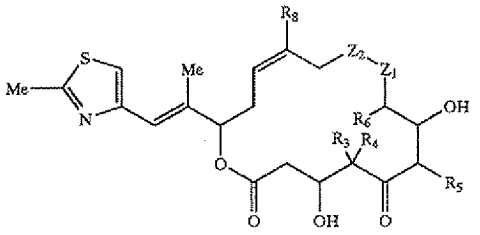
Scheme 18



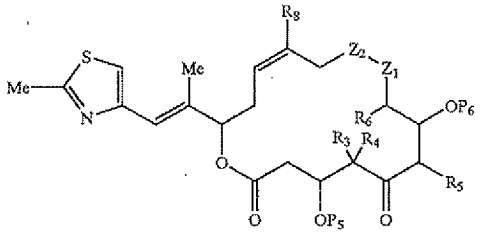
Similarly, a compound of formula V where Z_2 is NR_{23} can be prepared as shown in Scheme 17. A compound of formula LXIX can be prepared from a beta-amino ester LXXVIII and an allylating agent such as allylbromide. A compound of formula LXXIX can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXX. Alternatively, a compound of formula LXXX can be obtained from a compound of formula LXXIX by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXX can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXXI. Further elaboration of LXXXI as described above provides a compound of formula V where Z_2 is NR_{23}.

A compound of formula V where W is oxygen or NR_{15} and Y is H,H can be prepared as shown in Scheme 18. A compound of formula V can be converted to a compound of formula LXXII, where P_4 and P_5 are hydroxyl protecting groups, by treatment with a reagent such as t-butyldimethylsilyltriflate. A compound of formula LXXXIII can be prepared from a compound of formula LXXXII by treatment with Lawesson's reagent. A compound of formula LXXXIV can be prepared from a compound of formula LXXXIII by using a reducing agent such as tri-n-butyltin hydride when W is oxygen or by treatment

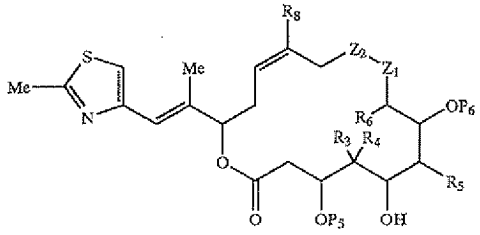
with methyl iodide and sodium borohydride when W is NR_{15}. Removal of the protecting groups from a compound of formula LXXXIV, using for example hydrogen fluoride when P_4 and P_5 are silyl groups, provides a compound of formula V where W is oxygen or NR_{15}, and Y is H,H.



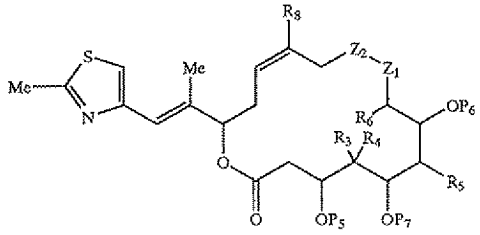
V



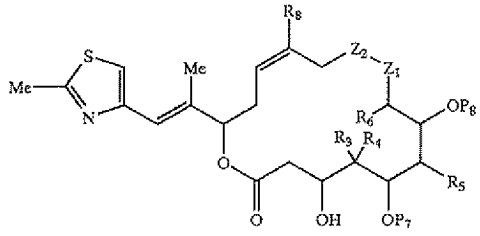
LXXXXV



LXXXXVI



LXXXXVII



LXXXXVIII

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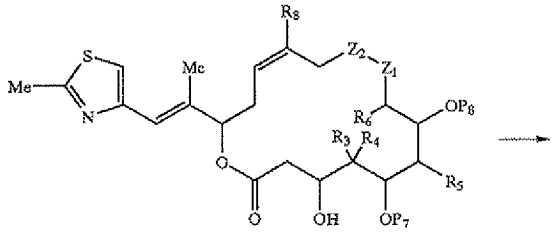
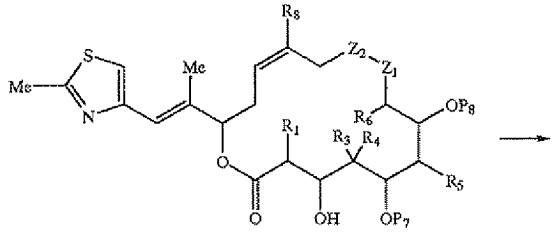
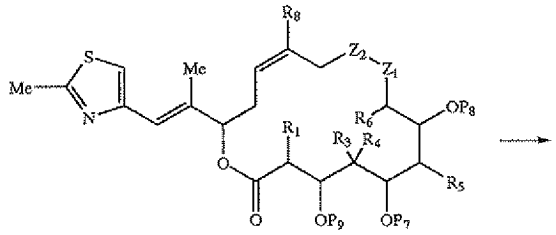


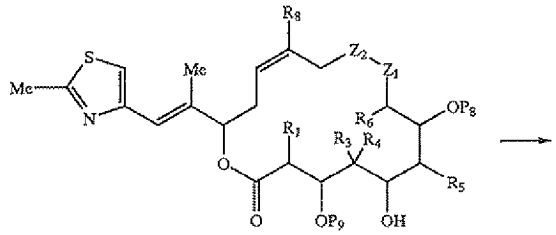
LXXXXIX



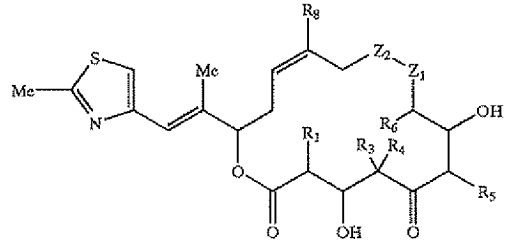
C



CI



CII

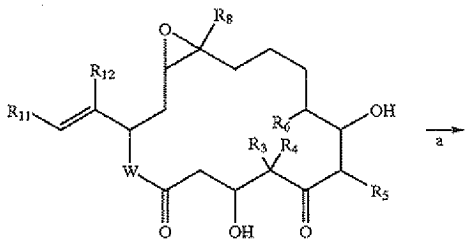


V

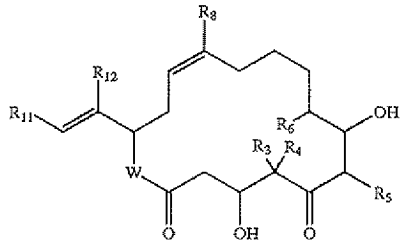
A compound of formula V where W and Y are oxygen, and R_1 is alkyl or substituted alkyl can be prepared as shown in Scheme 19. A compound of formula V can be protected to give a compound of formula LXXXV, where P_5 and P_6 are hydroxyl protecting groups, by treatment with a reagent such as t-butyldimethylsilyl trifluoromethanesulfonate. A compound of formula LXXXVI can be prepared from a compound of formula LXXXV by treatment with a reducing agent such as sodium borohydride. A compound of formula LXXXVII can be prepared from a compound of formula LXXXVI by protection of the hydroxyl group, where P_7 is

for example p-methoxybenzyl, using p-methoxybenzyl trichloroacetimidate. Removal of the protecting groups P_5 and P_6 of a compound of formula LXXXXVII using, for example, hydrogen fluoride in pyridine when P_5 and P_6 are t-butyldimethylsilyl groups provides a compound of formula LXXXXVIII which then can be selectively protected using for example t-butyldimethylsilyl chloride to give a compound of formula LXXXXIX where P_8 is a t-butyldimethylsilyl group. A compound of formula C can be prepared from a compound of formula LXXXXIX by treatment with a base such as lithium diisopropylamide followed by treatment with an alkylating agent such as methyl iodide. A compound of formula C can be protected to give a compound of formula CI, where P_9 is a hydroxyl protecting group, by treatment with a reagent such as t-butyldimethylsilyl trifluoromethanesulfonate. A compound of formula CII can be prepared from a compound of formula CI by removal of the P_7 group using, for example, DDQ when P_7 is a p-methoxybenzyl group. A compound of formula V, where W and Y are oxygen, and R_1 is alkyl or substituted alkyl, can be prepared from a compound of formula CII by oxidation using, for example, TPAP/NMO followed by removal of the protecting groups using, for example, hydrogen fluoride when P_8 and P_9 are silyl groups. This compound of formula V can be further oxidized with dimethyldioxirane as shown in Scheme 1 to provide the corresponding epoxide compound of formula V.

Scheme 20



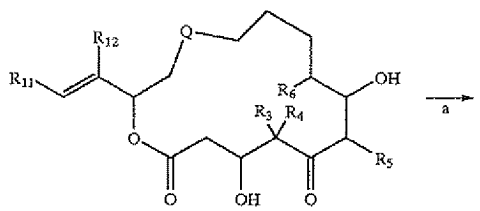
V(Q is oxirane group)



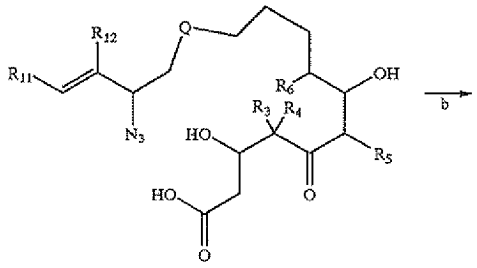
V(Q is ethylene group)

A compound of formula V where X is oxygen and Q is an olefin can be prepared from a compound of formula V where X is oxygen and Q is an oxirane ring by treatment with a reactive metallocene such as titanocene, zirconocene or niobocene as shown in Scheme 20 (see for example R. Schobert and U. Hohlein, *Synlett* (1990), 465–466.).

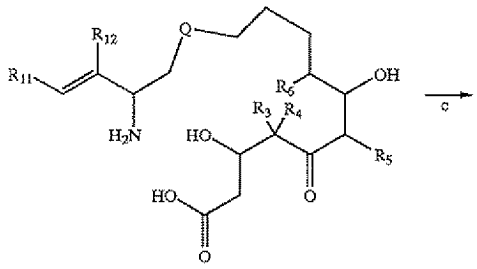
Scheme 21



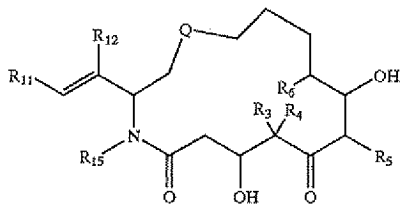
V (W is oxygen)



CIII



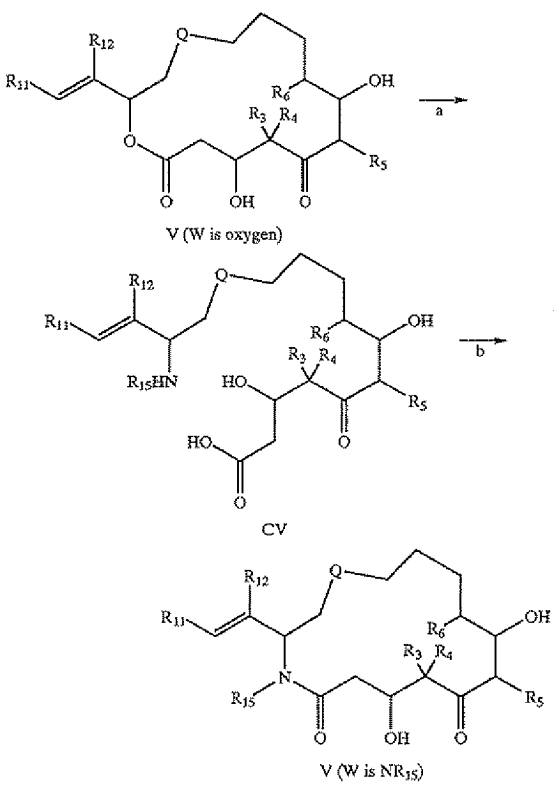
CIV



V (W is NR_{15})

A compound of formula V where X is oxygen and W is NR_{15}, where R_{15} is hydrogen, can be prepared from a compound of formula V where both X and W are oxygen as shown in Scheme 21. A compound of formula CIII can be prepared from a compound of formula V where both X and W are oxygen by formation of pi-allylpalladium complex using, for example, palladium tetrakistriphenylphosphine followed by treatment with sodium azide (see, for example: Murahashi, S.-I.; et. al. *J. Org. Chem.* 1989, 54, 3292). Subsequent reduction of a compound of formula CIII with a reducing agent such as triphenylphosphine provides a compound of formula CIV. A compound of formula V where X is oxygen and W is NR_{15}, where R_{15} is hydrogen, can be prepared from a compound of formula CIV by macrolactamization using, for example, diphenylphosphoryl azide or bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP).

Scheme 22



A compound of formula V where X is oxygen and W is NR_{15}, where R_{15} is alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, O-alkyl, O-substituted alkyl, can be prepared from a compound of formula V where both X and W are oxygen as shown in Scheme 22. A compound of formula CV can be prepared from a compound of formula V where both X and W are oxygen by formation of pi-allylpalladium complex using, for example, palladium tetrakistriphenylphosphine followed by treatment with a primary amine. A compound of formula V where X is oxygen and W is NR_{15}, where R_{15} is alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, OH, O-alkyl, O-substituted alkyl, can be prepared from a compound of formula V by macrolactamization using, for example, diphenylphosphoryl azide or bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP). In the case where R_{15} is OH, it may be necessary to remove a protecting group such as t-butyldimethylsilyl from an intermediate where R_{15} is O-t-butyldimethylsilyl.

The in vitro assessment of biological activity of the compounds of Formula V was performed as follows:

In vitro Tubulin Polymerization.

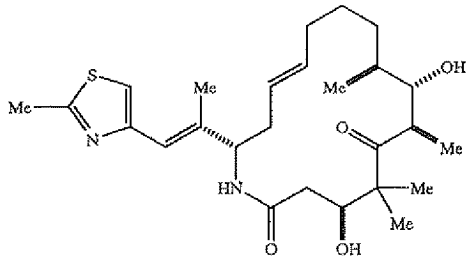
Twice cycled (2×) calf brain tubulin was prepared following the procedure of Williams and Lee (see Williams, R. C., Jr., and Lee, J. C. Preparation of tubulin from brain. Methods in Enzymology 85, Pt. D: 376–385, 1982) and stored in liquid nitrogen before use. Quantification of tubulin polymerization potency is accomplished following a modified procedure of Swindell, et al., (see Swindell, C. S., Krauss, N. E., Horwitz, S. B., and Ringel, I. Biologically active taxol analogues with deleted A-ring side chain substituents and variable C-2' configurations. J. Med. Chem. 34: 1176–1184, 1991). These modifications, in part, result in the expression of tubulin polymerization potency as an effective concentration for any given compound. For this method, different concentrations of compound in polymerization buffer (0.1M MES, 1 mM EGTA, 0.5 mM $MgCl_2$, pH 6.6) are added to tubulin in polymerization buffer at 37° in microcuvette wells of a Beckman (Beckman Instruments) Model DU 7400 UV spectrophotometer. A final microtubule protein concentration of 1.0 mg/ml and compound concentration of generally 2.5, 5.0, and 10 μM are used. Initial slopes of OD change measured every 10 seconds were calculated by the program accompanying the instrument after initial and final times of the linear region encompassing at least 3 time points were manually defined. Under these conditions linear variances were generally $<10^{-6}$, slopes ranged from 0.03 to 0.002 absorbance unit/minute, and maximum absorbance was 0.15 absorbance units. Effective concentration ($EC_{0.01}$) is defined as the interpolated concentration capable of inducing an initial slope of 0.01 OD/minute rate and is calculated using the formula: $EC_{0.01}$= concentration/slope. $EC_{0.01}$ values are expressed as the mean with standard deviation obtained from 3 different concentrations. $EC_{0.01}$ values for the compounds in this invention fall in the range 0.01–1000 μM.

Cytotoxicity (In-Vitro)

Cytoxicity was assessed in HCT-116 human colon carcinoma cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay as reported in T. L. Riss, et. al., "Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays.," *Mol. Biol. Cell* 3 (Suppl.):184a, 1992. Cells were plated at 4,000 cell/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37° form 72 hours at which time the tetrazolium dye, MTS at 333 μg/ml (final concentration), in combination with the electron coupling agent phenazine methosulfate at 25 μM (final concentration) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492 nM which can be quantitated spectrophotometrically. The greater the absorbance the greater the number of live cells. The results are expressed as an IC_{50}, which is the drug concentration required to inhibit cell proliferation (i.e. absorbance at 450 nM) to 50% of that of untreated control cells. The IC_{50} values for compounds of this invention fall in the range 0.01–1000 nM.

The following examples illustrate the present invention.

EXAMPLE 1



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione

A. N-[(2-Methyl)-1-propenyl]morpholine.

To stirring morpholine (165.5 g, 1.9 mol) was added isobutyraldehyde (173 mL, 1.9 mol) at a rate which did not allow the temperature of the reaction to exceed 30° C. After

complete addition, the reaction mixture was stirred at room temperature for 2 h, and then the flask was equipped with a Dean-Stark trap and heated at 160° C. for 20 h. The reaction mixture was then cooled to room temperature, and the flask was equipped with a vigreux column distillation apparatus. Distillation under high vacuum gave 135 g (50%) of Compound A as a clear colorless oil. MS (M+H, 142).

B. 2,2-Dimethyl-3-oxopentanal.

To a stirring solution of propionyl chloride (44 mL, 0.50 mol) in ether (135 mL) at 0° C. under nitrogen was added a solution of Compound A (69 g, 0.50 mol) in ether (135 mL) over 45 min. After addition was complete, the reaction mixture was stirred at reflux for 2 h, and then stirred at room temperature for 16 h. The reaction mixture was filtered, and the filter cake was washed with ether (50 mL). The volatiles were removed in vacuo. The residue was taken into H_2O (80 mL) and the solution was adjusted to a pH of 4. Ether was added (80 mL) and the biphasic mixture was stirred for 16 h. The reaction mixture was poured into a separatory funnel, the layers separated, and the aqueous layer was extracted with ether (5×100 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was distilled under high vacuum to give 10.4 g (16%) of Compound B as a clear, colorless oil. MS (M-H, 127).

C. 4-tert-Butyldimethylsilyloxy-5,5-dimethyl-6-oxo-1-octene.

To a solution of (−)-B-methoxydiisopinocamphenylborane (25.7 g, 81 mmol) in ether (80 mL) at 0° C. under nitrogen was added 1.0 M allylmagnesium bromide in ether (77 mL, 77 mmol) over 1.5 h. The reaction mixture was stirred at 25° C. for 1 h, and then concentrated in vacuo. The residue was extracted with pentane (2×150 mL), and the extracts were filtered through Celite under nitrogen. The combined extracts were then evaporated in vacuo to give the B-allyldiisopinocamphenylborane. This material was taken up in ether (200 mL) and cooled to −100° C. under nitrogen. A solution of Compound B (11.42 g, 89 mmol) in ether (90 mL) at −78° C. was then added over a 1 h period. The reaction mixture was stirred for an additional 0.5 h and methanol (1.5 mL) was added. The reaction mixture was brought to room temperature, treated with 3 N NaOH (32 mL) and 30% H_2O_2 (64 mL), and then kept at reflux for 2 h. The reaction mixture was cooled to room temperature, the layers were separated, and the organic phase was washed with H_2O (500 mL). The combined aqueous washes were re-extracted with ether (2×100 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. This residue was taken up in CH_2Cl_2 (250 mL), cooled to 0° C., and diisopropylethylamine (93 mL, 535 mmol) was added. To the stirring solution was then added tert-butyldimethylsilyl trifluoromethanesulfonate (69 g, 260 mmol) slowly as to not increase the temperature above 10° C. After complete addition, the reaction mixture was poured into H_2O (650 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×650 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes followed by 10% EtOAc/hexanes to give 17.2 g (78%) of Compound C as a clear, colorless oil. The enantiomeric excess was found to be 94% determined by ^1H NMR analysis of the Mosher's ester of the alcohol. ^{13}C NMR ($CDCl_3$, 80 MHz) d 215.8, 136.1, 116.5, 52.8, 39.0, 31.9, 26.0, 22.4, 20.1, 18.1, 7.6, −3.6, −4.4.

D. 3-tert-Butyldimethylsiloxy-4,4-dimethyl-5-oxoheptanal.

Through a solution of Compound C (10.8 g, 38.0 mmol) in CH_2Cl_2 at −78° C. was bubbled O_3 until the solution remained blue (1 h). O_2 was then bubbled through for 15 min followed by N_2 for 30 min after which time the solution became clear. Triphenylphosphine (10 g, 38 mmol) was then added and the reaction mixture was warmed to −35° C. and stored for 16 h. The volatiles were removed in vacuo and the residue was purified by flash chromatography eluting with 8% EtOAc/hexanes to give 8.9 g (74%) of Compound D as a clear, colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) d 9.75 (m, 1H), 4.53 (t, J=4.8 Hz, 1H), 3.40–3.60 (m, 4H), 1.10 (s, 3H), 1.07 (s, 3H), 0.98 (t, J=7.0 Hz, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

E. 3tert-Butyldimethylsiloxy-4,4-dimethyl-5-oxoheptanoic acid.

To a solution of Compound D (3.90 g, 13.6 mmol) in t-butanol (75 mL) was added 2-methyl-2-butene (5.85 mL, 55.2 mmol), and then a solution of sodium chlorite (4.61 g, 40.8 mmol) and sodium phosphate monobasic (2.81 g, 20.4 mmol) in H_2O (15 mL) was added dropwise at room temperature. The reaction mixture was stirred for 0.5 h and then the solvents were removed in vacuo. To the residue was added H_2O (150 mL) followed by extraction with EtOAc (3×150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes/1% AcOH to give 3.79 g (92%) of Compound E as a clear, colorless, viscous oil. MS (M+H, 303)

F. (R,R)-N-(2-Hydroxy-1-methyl-2-phenethyl)-N,2-(S)-dimethyl-6-hepteneamide.

A suspension of LiCl (6.9 g, 0.16 mol) and preformed lithium diisopropylamide (Aldrich, 2.0 M solution in heptane/ethylbenzene/THF, 27.6 mL, 55 mmol) in additional THF (70 mL) at −78° C. was treated dropwise with a solution of (R,R)-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl propionamide (6.0 g, 27 mmol, Meyers, A. G. et al. *J. Am. Chem. Soc.* 1994, 116, 9361) in THF (30 mL) over 10 min. The bright yellow, reaction mixture was stirred at −78° C. (1 h), at 0° C. (15 min), and at 25° C. (5 min) before being recooled to 0° C. and treated with a solution of 5-bromo-1-pentene (4.8 mL, 40 mmol) in THF (5 mL). The reaction mixture was stirred at 0° C. (24 h), poured into saturated aqueous NH_4Cl (100 mL) and EtOAc (100 mL). The two phases were separated and the aqueous phase was further extracted with EtOAc (3×100 mL). The organic extracts were combined, washed with saturated aqueous NaCl (200 mL), dried ($Na2SO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 4.0×25 cm, 2 % MeOH—$CHCl_3$) afforded Compound F (6.9 g, 88%) as a pale yellow oil. MS (ESI^+): 290 $(M+H)^+$; MS(ESI^-): 288.2 $(M-H)^-$.

G. (S)-2-Methyl-6-heptenol.

A 250 mL round-bottom flask at 0° C. was charged sequentially with pyrrolidine (2.6 mL, 30 mmol) and BH_3-THF complex (1.0 M in THF, 31 mL, 30 mmol). The borane-pyrrolidine complex was warmed to 25° C. (1 h), recooled to 0° C., and treated with n-butyllithium (1.6 M in hexane, 19 mL, 30 mmol) dropwise over 30 min while carefully maintaining an internal temperature below 5.5° C. The reaction mixture was stirred at 0° C. for an additional 30 min before a solution of Compound F (3.0 g, 10 mmol) in THF (23 mL) was added dropwise over 10 min. The reaction mixture was stirred at 25° C. (6 h) before being quenched by the dropwise addition of aqueous 3 N HCl (25 mL). The reaction mixture was then poured into aqueous 1 N HCl (200 mL) and extracted with Et_2O (4×80 mL). The combined organics were washed with a 1:1 solution of saturated aqueous NaCl-aqueous 1 N HCl (2×150 mL) and concentrated in vacuo. An aqueous solution of NaOH (1 N, 200

mL) was added to the residue and the suspension was stirred for 30 min. The mixture was extracted with Et_2O (3×100 mL) and the combined ether layers were washed with a 1:1 solution of saturated aqueous NaCl-aqueous 1 N NaOH (2×200 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 4.0×25 cm, 15–25% Et_2O-pentane gradient elution) afforded Compound G (1.26 g, 95%) as a colorless oil. $[a]^{25}D$-11 (c 12, CH_2Cl_2).

H. (S)-2-Methyl-6-heptenal.

A solution of Compound G (0.24 g, 1.9 mmol) in CH_2Cl_2 (6 mL) was treated with pyridinium chlorochromate (0.61 g, 2.8 mmol) and the reaction mixture was stirred at 25° C. for 5 h. The resulting dark brown viscous slurry was passed through a silica gel-Celite plug (Celite 1.0×1 cm on top of SiO_2, 1.0×5 cm, eluting with 50 mL of CH_2Cl_2). The solvent was removed in vacuo to afford crude Compound H (0.15 g, 63%) as a colorless oil, which was sufficiently pure to use in subsequent reactions. ^1H NMR (300 MHz, CD_2Cl_2) d 9.62 (s, 1H), 5.88–5.68 (m, 1H), 5.13–4.92 (m, 2H), 2.37–2.24 (m, 1H), 2.15–2.05 (m, 2H), 1.62–1.78 (m, 1H), 1.51–1.32 (m, 3H), 1.07 (d, 3H, J=7.0 Hz).

I. (3S,6R,7S,8S)-3-tert-Butyldimethylsiloxy-4,4,6,8-tetramethyl-7-hydroxy-5-oxo-12-tridecenoic acid.

To a preformed LDA solution (Aldrich, 2.0 M solution in heptane/ethylbenzene/THF, 3.8 mL, 7.6 mmol) in additional THF (25 mL) at −78° C. was added a solution of Compound E (1.0 g, 3.4 mmol) in THF (5 mL) dropwise over 3 min. The reaction mixture was stirred at −78° C. (10 min), warmed to −40° C. (20 min), and recooled to −78° C. before Compound H (0.56 g, 4.4 mmol) in THF (5 mL) was added. The reaction mixture was warmed to −40° C., stirred for 1 h, and diluted with saturated aqueous NH_4Cl (50 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (4×50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5×20 cm, 2–5% MeOH—$CHCl_3$ gradient elution) followed by HPLC (YMC S-10, ODS, 30×500 mm column, eluting with MeOH at a flow rate of 20 mL/min) separation afforded the desired syn-aldol product Compound I (0.60 g, 43%) and an undesired diastereomer (0.32 g, 22%) along with starting Compound E (~10%).

MS (ESI^+): 879.3 $(2M+Na)^+$, 451.2 $(M+Na)^+$, 429.2 $(M+H)^+$; MS(ESI^-): 427.3 $(M-H)^-$.

Stereochemistry was confirmed by direct comparison of both the ^{13}C and ^1H NMRs of the subsequent ester derivative (used in the synthesis of Epothilone C) to the same intermediate previously described by K. C. Nicolaou et al. *Angew. Chem. Int. Ed. Engl.* 1997, 36, 166.

J. (S)-2[N-[(tert-Butyloxy)carbonyl]amino]-4pentenoic acid.

A solution L-2-amino-4-pentenoic acid (NovaBiochem, 3.0 g, 26 mmol) in THF-H_2O (1:1, 200 mL) at 0° C. was treated sequentially with $NaHCO_3$ (6.6 g, 78 mmol) and di-tert-butyl dicarbonate (10.4 g, 1.8 mmol). The reaction mixture was warmed to 25° C. and stirred for 16 h. The pH of the mixture was adjusted to 4 by the careful addition of saturated aqueous citric acid at 0° C., and the mixture was extracted with EtOAc (4×50 mL). The combined organic layers were washed with saturated aqueous NaCl (75 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 4.0×6 cm, 5–10% MeOH—$CHCl_3$ gradient elution) afforded Compound J (5.5 g, 99%) as a colorless oil. MS(ESI^-): 429.3 $(2M-H)^-$, 214.1 $(M-H)^-$.

K. (S)-2-[N^2-[(tert-Butyloxy)carbonyl]amino]-N-methoxy-N-methyl-4-penteneamide.

A solution Compound J (2.9 g, 13 mmol) in $CHCl_3$ (55 mL) at 0° C. was treated sequentially with N,O-dimethylhydroxylamine hydrochloride (1.4 g, 15 mmol), 1-hydroxybenzotriazole (2.0 g, 15 mmol), 4-methylmorpholine (4.4 mL, 40 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.4 g, 18 mmol). The reaction mixture was gradually warmed to 25° C., stirred for 16 h, and diluted with H_2O (100 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (3×75 mL). The combined organic phases were washed with aqueous 5% HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3.0×20 cm, 25–50% EtOAc-hexane gradient elution) afforded Compound K (2.5 g, 71%) as a colorless oil. MS (ESI^+): 258.9 $(M+H)^+$, 202.9 (M-isobutylene), 158.9 (M-BOC); MS(ESI^-): 257.2 $(M-H)^-$.

L. (S)-3-[N-[(tert-Butyloxy)carbonyl]amino]-hexen-2-one.

A solution of Compound K (2.5 g, 1.0 mmol) in THF (65 mL) at 0° C. was treated with methylmagnesium bromide (3.0 M in Et_2O, 8.1 mL, 2.4 mmol). The reaction mixture was stirred at 0° C. (2.5 h) and carefully poured into saturated aqueous NH_4Cl (100 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (3×75 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (75 mL), H_2O (75 mL), saturated aqueous NaCl (75 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3.0×20 cm, 10–25% EtOAc-hexane gradient elution) afforded (S)-2-[N-[(tert-Butyloxy)carbonyl]amino]-5-hexene-2-one (2.2 g, 67%) as a colorless oil. MS (ESI^+): 213.9 $(M+H)^+$, 157.9 (M-isobutylene), 113.9 (M-BOC); MS(ESI^-): 212.2 $(M-H)^-$.

M. (S)-4-[3-[N-[(tert-Butyloxy)carbonyl]amino]-2-methyl-1(E),5-hexadienyl]-2-methylthiazole.

A solution of 2-methyl-4-thiazolylmethyl diphenylphosphine oxide (2.5 g, 8.0 mmol, Danishefsky et al. *J. Org. Chem.* 1996, 61, 7998) in THF (38 mL) at −78° C. was treated with n-butyllithium (1.6 M in hexane, 5.2 mL, 8.4 mmol) dropwise over 5 min. The resulting brilliant orange mixture was stirred for 15 min at −78° C., and treated with a solution of Compound L (0.81 g, 3.8 mmol) in THF (5 mL). After 10 min at −78° C., the cooling bath was removed and the reaction mixture was allowed to warm to 25° C. (2 h). The mixture was poured into saturated aqueous NH_4Cl (50 mL) and the two layers were separated. The aqueous phase was extracted with Et_2O (3×50 mL) and the combined organic extracts were washed successively with H_2O (75 mL), saturated aqueous $NaHCO_3$ (75 mL), saturated aqueous NaCl (75 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 4.0×30 cm, 10–20% EtOAc-hexane gradient elution) afforded Compound M (0.23 g, 18%) as a colorless oil along with recovered starting ketone (20–30%). MS (ESI^+): 309.1 $(M+H)^+$, 253.0 (M-isobutylene); MS(ESI^-): 307.3 $(M-H)^-$.

N. (S)-4-(3-Amino-2-methyl-1(E),5-hexadienyl)-2-methylthiazole.

Compound M (0.15 g, 0.49 mmol) was treated with 4.0 N HCl in 1,4-dioxane (5 mL) at 0° C. (30 min) under Ar. The volatiles were removed in vacuo, and the resulting white foam was dissolved in cold saturated aqueous $NaHCO_3$ (3 mL). The solution was extracted with EtOAc (4×10 mL), and the combined EtOAc layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1.0×5 cm, 5–10% MeOH—$CHCl_3$ gradient elution) afforded Compound N (88 mg, 88%) as a colorless oil. MS (ESI^+): 209.0 $(M+H)^+$; MS(ESI^-): 207.2 $(M-H)^-$.

O. (3S,6R,7S,8S)-N-(S)-[1-(2-Methyl-4-thiazolyl)-2-methyl-1(E),5-hexadien-3-yl]-3-tert-butyldimethylsiloxy-4,4,6,8-tetramethyl-7-hydroxy-5-oxo-12-trideceneamide.

A solution of Compound M (88 mg, 0.42 mmol) in DMF (1.3 mL) at 0° C. was treated sequentially with Compound I (0.15 g, 0.35 mmol), 1-hydroxybenzotriazole (49 mg, 0.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.10 g, 0.52 mmol). The reaction mixture was gradually warmed to 25° C., stirred for 15 h, and diluted with H_2O (3 mL). The mixture was extracted with EtOAc (3×10 mL), an the combined organic phases were washed with aqueous 5% HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5×20 cm, 2.5% MeOH—$CHCl_3$) afforded Compound O (0.17 g, 77%) as a white foam. MS (ESI^+): 619.3 $(M+H)^+$.

P. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4tert-Butyldimethylsiloxyhydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione.

A solution of Compound O (17 mg, 27 mmol) in degassed benzene (8.0 mL) was treated with Grubb's catalyst [bis (tricyclohexylphosphine)benzylidine ruthenium dichloride, Strem Chemicals, 11 mg, 14 mmol) under Ar. The reaction mixture was stirred at 25° C. for 15 h and treated again with an additional portion of catalyst (5.0 mg, 4.5 mmol). After 7 additional hours, the benzene was removed in vacuo, and the black viscous residue was passed through a pad of silica gel (1.0×3 cm) eluting with Et_2O (25 mL). The eluent was concentrated in vacuo to afford a separable 5:1 (E/Z) mixture of geometric isomers. PTLC (SiO_2, 1 mm plate, 2 elutions with a 1:1:1 solution of hexane-toluene-ethyl acetate) afforded the E-isomer Compound P (5.1 mg, 34%) and the corresponding Z-isomer (1.0 mg, 6.7%). For Compound P: MS (ESI^+): 1181.7 $(2M+H)^+$, 591.4 $(M+H)^+$. For the Z-isomer: MS (ESI^+): 1181.5 $(2M+H)^+$, 613.2 $(M+Na)^+$, 591.2 $(M+H)^+$; MS (ESI^-): 589.3 $(M-H)^-$.

Q. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione.

To a 1 dram vial charged with Compound P (2.3 mg, 3.9 mmol) in CH_2Cl_2 (0.4 mL) at 0° C. was added trifluoroacetic acid (0.1 mL). The reaction mixture was sealed under a blanket of Ar and stirred at 0° C. After 4 h, the volatiles were removed under a constant stream of Ar at 0° C. Saturated aqueous $NaHCO_3$ (1 mL) and EtOAc (1 mL) were added to the residue and the two layers were separated. The aqueous phase was extracted with EtOAc (4×1 mL), and the combined EtOAc layers were dried (Na_2SO_4) and concentrated in vacuo. PTLC (SiO_2, 20×10×0.025 cm, eluting with 5% MeOH—$CHCl_3$) afforded [4S-[4R*,7S*,8S*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione (1.3 mg, 68%) as a white film. MS (ESI^+): 953.5 $(2M+H)^+$, 477.3 $(M+H)^+$; MS (ESI^-): 475.5 $(M-H)^-$.

EXAMPLE 2

The following compounds can be made following the reaction schemes previously disclosed:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;]

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-_cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;]

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-10-aza-1-oxa-13-_ cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

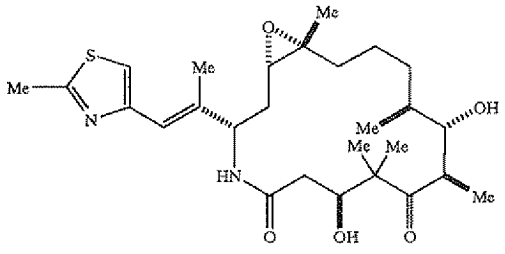
[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide.

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione.

[1S-[R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione.

EXAMPLE 3



[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0] heptadecane-5,9-dione.

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-12,13-epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-16-heptadecenoic acid.

A solution of epothilone B (0.35 g, 0.69 mmol) in degassed THF (4.5 mL) was treated with a catalytic amount (80 mg, 69 mmol) of tetrakis(triphenylphosphine) palladium (0) and the suspension was stirred at 25° C., under Ar for 30 min. The resulting bright yellow, homogeneous solution was treated all at once with a solution of sodium azide (54 mg, 0.83 mmol) in degassed H_2O (2.2 mL). The reaction mixture was warmed to 45° C. for 1 h, diluted with H_2O (5 mL) and extracted with EtOAc (4×7 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3.0×15 cm, 95:5.0:0.5 $CHCl_3$—MeOH—AcOH) to afford Compound A (0.23 g, 61%) as a colorless oil. MS (ESI^+): 551 $(M+H)^+$; MS(ESI^-): 549 $(M-H)^-$.

B. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-12,13epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-16-heptadecenoic acid.

A solution of Compound A (0.23 g, 0.42 mmol) in THF (4.0 mL) was treated with H_2O (23 mL, 1.25 mmol) and polymer supported triphenylphosphine (Aldrich, polystyrene cross-linked with 2% DVB, 0.28 g, 0.84 mmol) at 25° C. The resulting suspension was stirred at 25° C. under Ar (32 h), filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1.5×10 cm, 95:5.0:0.5 to 90:10:1.0 $CHCl_3$—MeOH—AcOH gradient elution) to afford Compound B (96 mg, 44%) as a colorless oil. MS (ESI^+): 525.2 $(M+H)^+$; MS(ESI^-): 523.4 $(M-H)^-$.

Alternatively, to a 25 mL round-bottom flask charged with Compound A (0.26 g, 0.47 mmol) and PtO_2 (0.13 g, 50 wt %) was added absolute EtOH under Ar. The resulting black mixture was stirred under one atmosphere of H_2 for 10 h, after which time the system was purged with N_2 and an additional portion of PtO_2 (65 mg, 25 wt %) was added. Once again the reaction mixture was stirred under a blanket of H_2 for 10 h. The system was then purged with N_2, and the reaction mixture was filtered through a Celite pad eluting with CH_2Cl_2 (3×25 mL). The solvents were removed in vacuo and the residue was purified as described above to afford Compound B (0.19 g, 75%).

Alternatively, a solution of Compound A (20 mg, 36 mmol) in THF (0.4 mL) was treated with triphenylphosphine (19 mg, 73 mmol) under Ar. The reaction mixture was warmed to 45° C., stirred for 14 h and cooled to 25° C. The resulting iminophosphorane was treated with ammonium hydroxide (28%, 0.1 mL) and once again the reaction mixture was warmed to 45° C. After 4 h, the volatiles were removed in vacuo and the residue was purified as described above to afford Compound B (13 mg, 70%).

C. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0] heptadecane-5,9-dione.

A solution of Compound B (0.33 g, 0.63 mmol) in degassed DMF (250 mL) was treated with solid $NaHCO_3$ (0.42 g, 5.0 mmol) and diphenylposphoryl azide (0.54 mL, 2.5 mmol) at 0° C. under Ar. The resulting suspension was stirred at 4° C. for 24 h, diluted with phosphate buffer (250 mL, pH=7) at 0° C. and extracted with EtOAc (5×100 mL). The organic extracts were washed with 10% aqueous LiCl (2×125 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was first purified by flash chromatography (SiO_2, 2.0×10 cm, 2–5% MeOH—$CHCl_3$ gradient elution) and

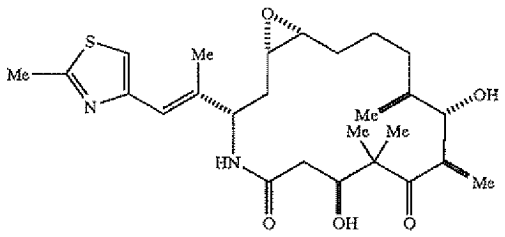
then repurified using a Chromatotron (2 mm SiO_2, GF rotor, 2–5% MeOH—$CHCl_3$ gradient elution) to afford the title compound (0.13 g, 40%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (s, 1H), 6.71 (d, 1H, NH, J=8.1 Hz), 6.56 (s, 1H), 4.69–4.62 (m, 1H), 4.18–4.12 (m, 1H), 4.01–3.96 (m, 1H), 3.86 (s, 1H), 3.38–3.34 (m, 1H), 2.82 (dd, 1H, J=5.6, 6.0 Hz), 2.71 (s, 3H), 2.58 (s, 1H), 2.43 (dd, 1H, J=9.0, 14.5 Hz), 3.34 (dd, 1H, J=3.0, 14.5 Hz), 2.14 (s, 3H), 2.05–1.92 (m, 2 H), 1.82–1.41 (a series of multiplets, 7H), 1.35 (s, 3H), 1.28 (s, 3H), 1.18 (d, 3H, J=6.8 Hz), 1.14 (s, 3H), 1.00 (d, 3H, J=6.8 Hz); MS (ESI^+): 507.2 $(M+H)^+$; MS(ESI^-): 505.4 $(M-H)^-$.

EXAMPLE 4

Process for reduction of oxirane ring of epothilone and epothilone analogs.

To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis (cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with argon. The red suspension became dark, turning a homogeneous deep green after 1.5 h with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 eq) was removed and cooled to −78 ° C. under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 eq). The reaction mixture was warmed to room temperature and stirred for 15 min. The volatiles were removed in vacuo and the residue was chromatographed two times on silica (25 g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of epothilone C as a pale yellow viscous oil.

EXAMPLE 5



[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0] heptadecane-5,9-dione.

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-3,7-dihydroxy-12,13-epoxy-4,4,6,8,16-pentamethyl-17-(2-methyl-4-thiazolyl)oxo-16(E)-heptadecenoic acid.

Tetrakis(triphenylphosphine)palladium(0) (1.17 g, 1.01 mmol, 0.10 eq) was added to a solution of epothilone A (4.97 g, 10.1 mmol, 1.0 eq) in degassed THF (100 ml) at room temperature and was stirred for 30 minutes under argon. Sodium azide (0.980 g, 15.1 mmol, 1.5 eq) was added to the above reaction mixture followed by the addition of degassed water (10 ml). The reaction mixture was heated to 45° C. for one hour, cooled to room temperature, diluted with ethyl acetate (300 ml) and further diluted with water (150 ml). The aqueous layer was extracted with ethyl acetate (3×100 ml). The combined organic extracts were washed with brine (150 ml), dried (sodium sulfate), filtered and concentrated under vacuum. The oily residue was purified by flash silica gel chromatography (eluting 0–5% methanol/chloroform with 0.1% of acetic acid) to afford Compound A (1.84 g, 34.0% yield) as glassy solid. MS (ESI^+): 537 $(M+H)^+$; MS (ESI^-): 535 $(M-H)^-$

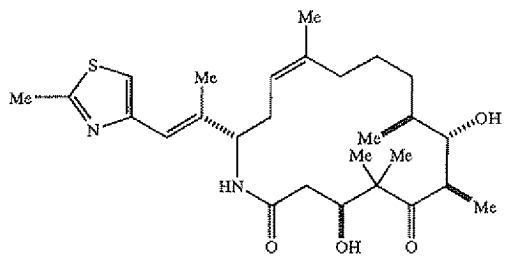
B. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-3,7-dihydroxy-12,13-epoxy-4,4,6,8,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid.

Platinum oxide (0.980 g, 4.30 mmol, 1.25 eq) was added to a solution of Compound A (1.85 g, 3.44 mmol, 1.0 eq) in absolute ethanol (137 ml). The reaction mixture was stirred vigorously under a hydrogen balloon for 16 hours at room temperature. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The oily residue was purified by preparative HPLC (YMC S-15 ODS 50×500 mm column, 45 minutes/gradient, 0–100% B, 50 ml/min, retention time=17 minutes, A=0.1% acetic acid /5% acetonitrile/95% water, B=0.1% acetic acid/5% water/95% acetonitrile). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford Compound B (1.33 g, 76.0% yield) as a colorless solid. MS (ESI^+): 511$(M+H)^+$; MS (ESI^-): 509 $(M-H)^-$

C. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0] heptadecane5,9-dione.

Compound Compound B (0.860 g, 1.68 mmol, 1.0 eq) was dissolved in anhydrous DMF (0.00250M, 672 ml) and degassed for one hour at room temperature. The solution was cooled to 0° C., and anhydrous sodium bicarbonate (1.13 g, 13.4 mmol, 4.0 eq) and diphenylphosphoryl azide (1.85 g, 6.72 mmol, 8.0 eq) were added under argon. The reaction mixture was kept at 4° C. under argon and stirred 16 hours. The reaction mixture was then cooled to −60° C., and pH 7 phosphate buffer (400 ml) was added slowly to quench the reaction. Temperature was kept below −30° C. The above mixture was allowed to warm to room temperature slowly and extracted with ethyl acetate (1 liter). The aqueous layer was washed with ethyl acetate (4×300 ml). The organic extracts were combined, washed with 10% LiCl (500 ml), dried (sodium sulfate), filtered and concentrated under vacuum. The oily residue was purified by preparative HPLC (YMC S-15 ODS 50×500 mm column, 45 minutes/gradient, 0–100% B, 50 ml/min, retention time=35 minutes, A=5% acetonitrile/95% water, B=5% water/95% acetonitrile). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford title compound (0.220 g, 26.0% yield) as a colorless solid. MS (ESI^+): 493 $(M+H)^+$; MS (ESI^-): 491 $(M-H)^-$

EXAMPLE 6

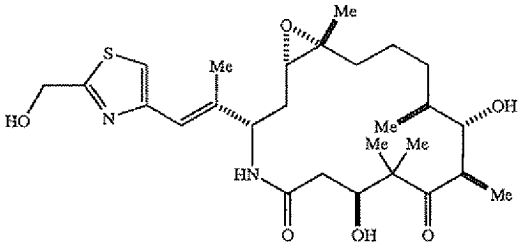


[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6dione.

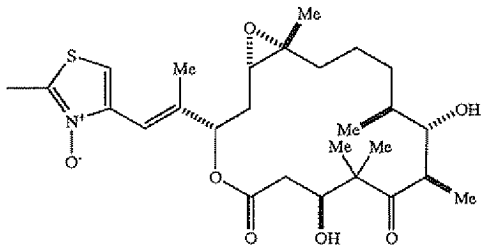
Tungsten hexachloride (0.19 g, 0.49 mmol, 0.5 equiv) was dissolved in THF (5.0 ml) and the solution was cooled to

−78° C. n-Butyllithium in hexane (1.6M, 0.63 ml, 1.0 mmol, 1.0 equiv) was added in one portion and the reaction mixture was allowed to warm to room temperature over 20 minutes (the solution turned dark green upon warming to rt). A 0.1M solution of the prepared tungsten reagent (0.79 ml, 0.079 mmol, 2.0 mmol) was added to Compound 4C (0.020 g, 0.039 mmol, 1.0 equiv) at room temperature. The reaction mixture was stirred a room temperature for 30 minutes and then was quenched with saturated $NaHCO_3$ (2.0 ml). The quenched solution was diluted with water (10 ml) and the solution was extracted with CH_2Cl_2 (4×20 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum. The inorganics were removed by passing the residue through a silica gel plug (eluting with 19/1 $CHCl_3$/MeOH). The eluent was concentrated under vacuum. The residue was purified by phplc (YMC-S5 ODS, 30–100% B, A=5% aq CH_3CN, B=95% aqueous CH_3CN, 3 ml/min., 220 nm., 30 min. gradient) and the appropriate fractions were concentrated under vacuum. The sticky solid was lyophilized from aqueous acetonitrile to afford title compound (4.3 mg, 29%) as a white solid. TLC: Rf=0.57 (9/1 CHCl3/MeOH, visualization by UV); HRMS: (M+H)+ calc=491.29436, found=491.2934

EXAMPLE 7

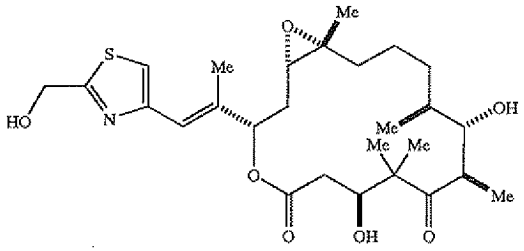


[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo [14.1.0]heptadecane-5,9-dione.

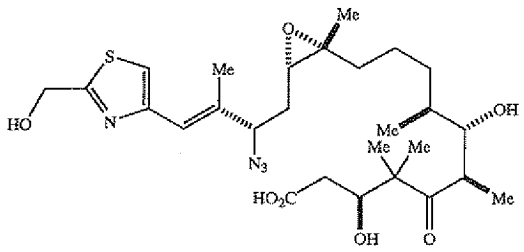


A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0] heptadecane-5,9-dione, N-oxide.

A solution of epothilone B (2.0 g, 3.9 mmol) in CH_2Cl_2 (30 mL) was treated with 3-chloroperoxybenzoic acid (1.0 g, 5.9 mmol) at 25° C., under Ar for 2 h. An additional 0.5 g (3.0 mmol) of 3-chloroperoxybenzoic acid was added and the reaction mixture was then stirred for 2 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (75 mL), 5% aqueous Na_2SO_3 (75 mL), H_2O (75 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 4.5×30 cm, 2–10% MeOH—$CHCl_3$ gradient elution) to afford Compound A (1.04 g, 50%) as a white solid. MS (ESI^+): 524.3 $(M+H)^+$; MS (ESI^-): 522.5 $(M-H)^-$.

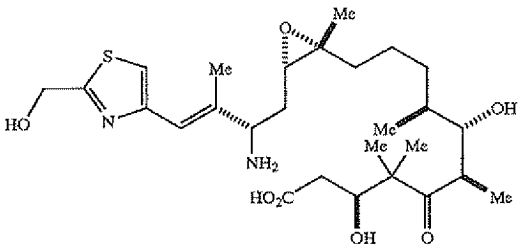


B. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione, [Epothilone F]. To a solution of compound A (0.46 g, 0.88 mmol) in CH_2Cl_2 (10 mL) in a resealable tube was added 2,6-lutidine (0.82 mL, 7.0 mmol) and trifluoroacetic anhydride (0.87 mL, 6.2 mmol) under Ar. The reaction vessel was sealed under Ar, heated to 75° C. (12 min), cooled to 25° C., and the volatiles were removed under a steady stream of N_2. The reaction tube was then placed on a high vacuum pump for 15 min. The resulting residue was dissolved in MeOH (10 mL) and treated with ammonium hydroxide (28–30% NH_4 in H_2O, 1.0 mL). The mixture was heated to 45° C. (10 min), and the volatiles were removed in vacuo. The crude reaction mixture was purified by HPLC (YMC S-15 ODS 30×500 mm column, 50% acetonitrile-H_2O isocratic conditions, flow rate=20 mL/min, retention time=28 min). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford Compound B (0.22 g, 48%) as a white solid. MS (ESI^+): 524.3 $(M+H)^+$, 1047.6 $(2M+H)^+$; MS (ESI^-): 522.5 $(M-H)^-$.

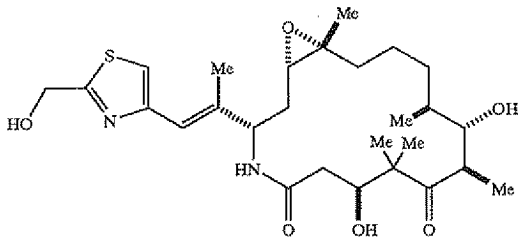


C. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-3,7-Dihydroxy-12,13-epoxy-4,4,6,8,12,16-hexamethyl-17-(2-hydroxymethyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid. A solution of Compound B (0.18 g, 0.34 mmol) in degassed THF (3.0 mL) was treated with a catalytic amount (40 mg, 3.4×10^{-2} mmol) of tetrakis(triphenylphosphine) palladium(0) and the suspension was stirred at 25° C., under Ar for 30 min. The resulting bright yellow, homogeneous solution was treated all at once with a solution of sodium azide (27 mg, 0.41 mmol) in degassed H_2O (1.5 mL). The reaction mixture was warmed to 45° C. for 1 h, diluted with H_2O (5 mL) and extracted with EtOAc (4×10 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The

residue was purified by flash chromatography (SiO_2, 2.5×15 cm, 95:5 $CHCl_3$—MeOH to 95:5.0:0.5 $CHCl_3$—MeOH—AcOH gradient elution) to afford Compound C (39 mg, 20%) as a colorless oil. MS (ESI^+): 567.4 $(M+H)^+$, 1133.6 $(2M+H)^+$; MS (ESI^-): 565.5 $(M-H)^-$, 1131.8 $(2M-H)^-$.



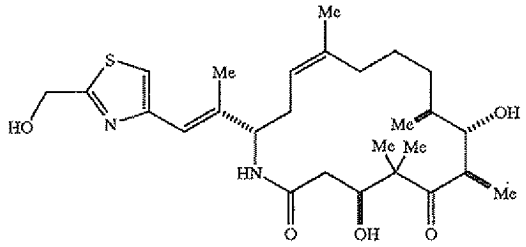
D. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-3,7dihydroxy-12,13-epoxy-4,4,6,8,12,16-hexmethyl-17-(2-hydroxymethyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid. To a 10 mL round-bottom flask charged with compound C (40 mg, 71 mmol) and PtO_2 (12 mg, 30 wt %) was added absolute EtOH (3 mL) under Ar. The resulting black mixture was stirred under one atmosphere of H_2 for 10 h. The system was then purged with N_2 and the reaction mixture was filtered through a nylon membrane (washing with 25 mL of MeOH). The solvents were removed in vacuo to afford Compound D (29 mg, 76%) as a foam, which was sufficiently pure to use in the next step. LCMS: 541.3 $(M+H)^+$.



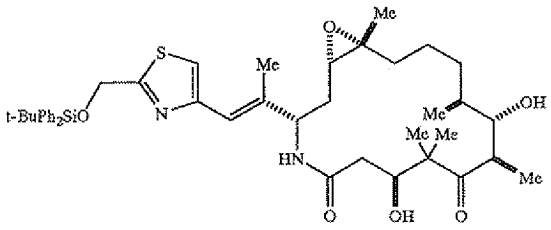
E. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo [14.1.0]heptadecane-5,9-dione.

A solution of compound D (29 mg, 54 mmol) in degassed DMF (21 mL) was treated with solid $NaHCO_3$ (36 mg, 0.43 mmol) and diphenylphosphoryl azide (46 mL, 0.21 mmol) at 0° C. under Ar. The resulting suspension was stirred at 4° C. for 19 h, cooled to −40° C., diluted with 25 mL of pH 7 phosphate buffer (carefully adding such that the internal temperature remains below −30 ° C.), and extracted with EtOAc (4×10 mL). The organic extracts were washed with cold 10% aqueous LiCl (25 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified using a chromatotron (1 mm SiO_2 GF rotor, 2–5% MeOH—$CHCl_3$ gradient elution) to afford the title Compound E (9.1 mg, 34%) as a colorless oil. MS (ESI^+): 523.2 $(M+H)^+$; MS (ESI^-): 521.5 $(M-H)^-$.

EXAMPLE 8

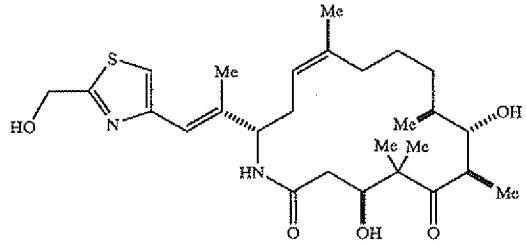


[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione.



A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-tert-butyldiphenylsilyloxymethyl-4-thiolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-6,9-dione.

A solution of Compound 7E (6.8 mg, 13 mmol) in CH_2Cl_2 (0.5 mL) was treated with triethylamine (2.7 mL, 20 mmol), 4-N,N-dimethylaminopyridine (0.2 mg, 1.3 mmol) and tert-butyldiphenylsilyl chloride (3.7 mL, 14 mmol) at 0° C. under Ar. The reaction mixture was gradually warmed to 25° C. (1 h), cooled to 0° C., quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), and extracted with EtOAc (4×2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1.0×5 cm, 2–5% MeOH—$CHCl_3$ gradient elution) to afford Compound A (7.0 mg, 71%) as a colorless oil. MS (ESI^+): 761.5 $(M+H)^+$; MS (ESI^-): 759.7 $(M-H)^-$.



B. [4S-[4R*,7S*,8R*,9R*,16R*(E)]]-4,8-Dihydroxy-5,6,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione.

A solution of tungsten(IV) chloride (0.10 g, 0.25 mmol) in anhydrous THF at −78° C. was treated with n-BuLi (1.6 M in hexanes, 0.32 mL, 0.50 mmol) under Ar. The reaction mixture was warmed to 25° C. over 40 min and then recooled to 0° C. An aliquot of the resulting deep-green, homogeneous solution (0.2 mL, 20 mmol) was added to a 1 dram vial charged with compound A (7.0 mg, 9.2 mmol) at

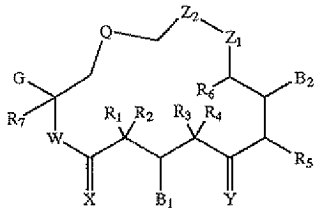
0° C. under Ar. The reaction mixture was warmed to 25° C., stirred for 30 min, quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL) and extracted with EtOAc (4×1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, 20×20×0.025 cm, eluting with 5% MeOH—$CHCl_3$) to afford an inseparable mixture of the silyl-protected (13Z) isomer of Compound B along with a small amount (<10%) of the minor (13E) isomer, which was immediately deprotected in the next step.

The silyl-protected isomeric mixture of compound B (2.3 mg, 3.1 mmol) was treated with 0.3 mL of a buffered solution of HF-pyridine in THF (2:1:0.5 THF/pyridine/HF-pyridine solution from Aldrich Chemical Co.) at 25° C. After 1 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (0.5 mL) and extracted with EtOAc (4×1 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 mL), dried (Na_2SO_4) and the volatiles were removed in vacuo. The residue was purified by preparative TLC (SiO_2, 20×10×0.025 cm, eluting with 5% MeOH—$CHCl_3$) to afford title compound (13Z-isomer) along with an inseparable amount (<10%) of the minor (13E) isomer (0.96 mg, 20% for the two steps) as a thin film. MS (ESI^+): 507.3 $(M+H)^+$; MS (ESI^-): 505.6 $(M-H)^-$.

What is claimed:

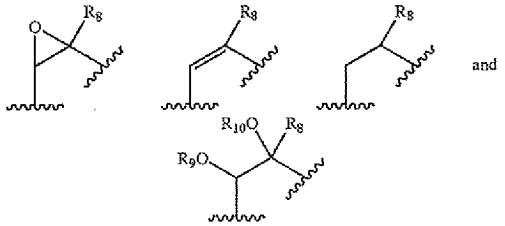
1. A compound of the formula:

V



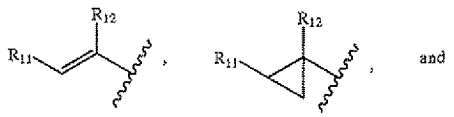
wherein:

Q is selected from the group consisting of:



and

G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



and

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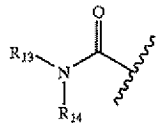


W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H,$NHOR_{19}$; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O—C(═O)—$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

$R_6$is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C$═O; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts thereof, hydrates, solvates or geometric, optical or stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

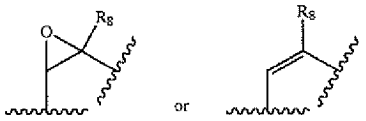
R_8 is H or methyl; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above are excluded.

2. The compound of claim 1 wherein

Q is



X is O;

Y is O;

Z_1, and Z_2, are CH_2; and

W is NR_{15}.

3. A compound selected from the group consisting of:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-

methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7, 9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7, 9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl) ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7, 11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4, 17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7, 11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo [14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7, 9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2, 6-dione;

and the pharmaceutically acceptable salts, solvates and hydrates thereof.

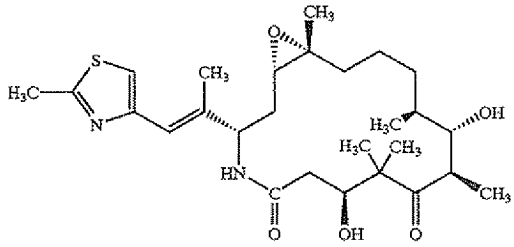
4. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **1**.

5. The method of claim **4**, wherein the cancer is cancer of the breast, ovary, or colon.

6. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **2**.

7. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **3**.

8. A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer or stereoisomer thereof.

9. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **8**.

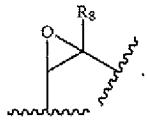
10. The method of claim **9**, wherein the cancer is cancer of the breast, ovary, or colon.

11. The method of claim **6**, wherein the cancer is cancer of the breast, ovary, or colon.

12. The method of claim **7**, wherein the cancer is cancer of the breast, ovary, or colon.

13. The compound of claim **1**, wherein G is 1-methyl-2-(substituted-4-thiazolyl) ethenyl group.

14. The compound of claim **1**, wherein Q is



15. The compound of claim **1**, wherein W is NR_{15}.

16. The compound of claim **1**, wherein X and Y are each O.

17. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **13**.

18. The method of claim **17**, wherein the cancer is cancer of the breast, ovary, or colon.

19. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **14**.

20. The method of claim **19**, wherein the cancer is cancer of the breast, ovary, or colon.

21. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **15**.

22. The method of claim **21**, wherein the cancer is cancer of the breast, ovary, or colon.

23. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 16.

24. The method of claim 23, wherein the cancer is cancer of the breast, ovary, or colon.

25. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

26. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 2.

27. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 3.

28. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 8.

29. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 13.

30. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 14.

31. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 15.

32. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 16.

33. The method of claim 4, further comprising administering one or more of an additional anti-cancer agent.

34. The method of claim 33, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

35. The method of claim 34, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

36. The method of claim 4, further comprising administering radiation therapy.

37. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable vehicle or diluent.

38. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable vehicle or diluent.

39. A pharmaceutical composition comprising the compound of claim 3 and a pharmaceutically acceptable vehicle or diluent.

40. A pharmaceutical composition comprising the compound of claim 8 and a pharmaceutically acceptable vehicle or diluent.

41. A pharmaceutical composition comprising the compound of claim 13 and a pharmaceutically acceptable vehicle or diluent.

42. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable vehicle or diluent.

43. A pharmaceutical composition comprising the compound of claim 15 and a pharmaceutically acceptable vehicle or diluent.

44. A pharmaceutical composition comprising the compound of claim 16 and a pharmaceutically acceptable vehicle or diluent.

45. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

46. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

47. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

48. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 8.

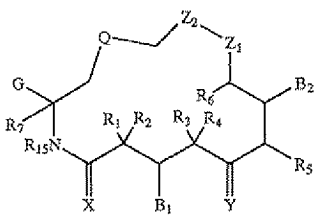
49. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 13.

50. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

51. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 15.

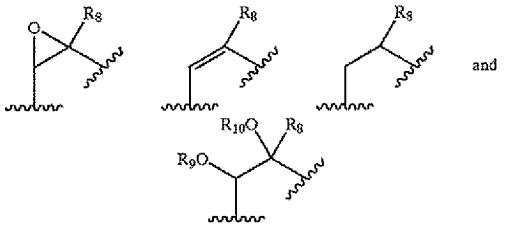
52. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 16.

53. A compound of the formula:



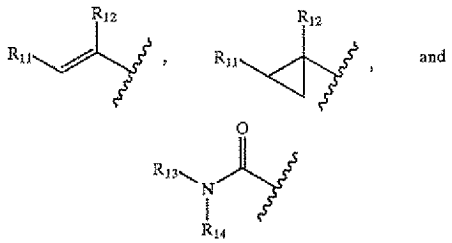
wherein:

Q is selected from the group consisting of:



and

G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



and

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, $NHOR_{19}$; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O—C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C{=}O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof.

54. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **53**.

55. The method of claim **54** wherein the cancer is cancer of the breast, ovary, or colon.

56. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim **53**.

57. The method of claim **54** further comprising administering one or more of an additional anti-cancer agent.

58. The method of claim **57** wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

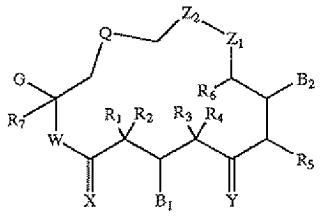
59. The method of claim **58** wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

60. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim **53**.

61. A pharmaceutical composition comprising the compound of claim **53** and a pharmaceutically acceptable vehicle or diluent.

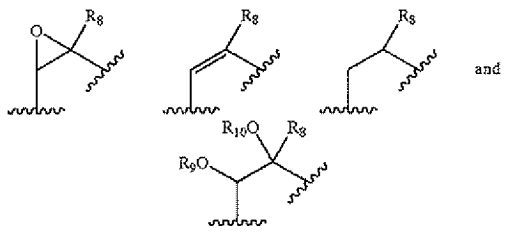
62. A compound of the formula:

V



wherein:

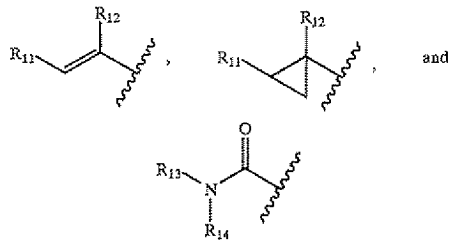
Q is selected from the group consisting of:



and

G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15

membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, $NHOR_{19}$; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O—C(═O)—$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3–C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C$═O; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof;

wherein substituted alkyl is an alkyl group substituted with from one to four substituents selected from the group consisting of halo; trifluoromethyl; trifluoromethoxy; hydroxy; alkoxy; cycloalkoxy; heterocyclooxy; oxo; alkanoyl; aryloxy; alkanoyloxy; amino; alkylamino; arylamine; aralkylamino; cycloalkylamino; heterocycloamino; disubstituted amines wherein the substituents are selected from alkyl, aryl, and aralkyl; alkanoylamino; optionally substituted with halogen, alkyl, alkoxy, aryl, or araralkyl; arylamino optionally substituted with halogen, alkyl, alkoxy, aryl, or araralkyl; aralkanoylamino optionally substituted with halogen, alkyl, alkoxy, aryl, or araralkyl; thio; alkylthio; aralkylthio; cycloalkylthio; heterocyclothio; alkylthiono; arylthiono; aralkylthiono; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; sulfonamido optionally substituted with halogen, alkyl, alkoxy, aryl, or araralkyl; nitro; cyano; carboxy; carbamyl optionally substituted with halogen, alkyl, alkoxy, aryl, or araralkyl; alkoxycarbonyl; aryl; substituted aryl; guanidino; and heterocyclo; and

substituted aryl is an aryl group substituted with from one to four substituents selected from the group consisting of alkyl; substituted alkyl; halo; trifluoromethyl; trifluoromethoxy; hydroxy; alkoxy; cycloalkoxy; heterocyclooxy; alkanoyl; alkanoyloxy; amino; alkylamino; aralkylamino; cycloalkylamino; heterocycloamino; dialkylamino; alkanoylamino; thio; alkylthio; cycloalkylthio; heterocyclothio; ureido; nitro; cyano; carboxy; carboxyalkyl; carbamyl; alkoxycarbonyl; alkylthiono; arylthiono; alkylsulfonyl; sulfonamido; and aryloxy each of which may be optionally substituted with halo, hydroxy, alkyl, alkoxy, substituted aryl, substituted alkyl, or substituted aralkyl;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above are excluded.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

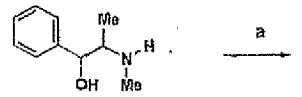
PATENT NO. : 6,605,599 B1
DATED : August 12, 2003
INVENTOR(S) : Gregory D. Vite et al.

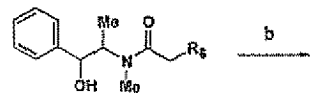
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 6, the text "which claims" should appear -- and claims --.
Line 42, the reference numeral "V" should appear in the center of the column following the chemical formula at col. 1, lines 42-50.

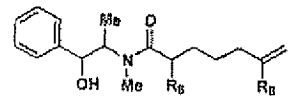
Column 6,
Line 59, insert the text: —Q is —.

Column 10,
Lines 1-20, the formulae designated pseudoephedrine, XXVI and XXVII should appear as follows:





XXVI



XXVII

Column 11,
Line 44, the text "XXI" should appear -- XXXI --.
Line 51, the text "XXII" should appear -- XXXII --.
Line 55, the text "XXIII" should appear -- XXXIII --.

Column 12,
Line 64, the text "XXXVI" should appear -- XXXVII --.

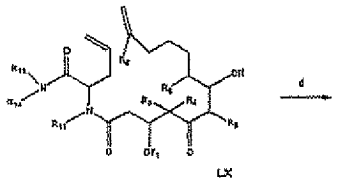
Column 13,
Line 1, the text "XXXVIII" should appear -- XXXVII --.
Line 15, the text "XXX" should appear -- XXXX --.

CERTIFICATE OF CORRECTION

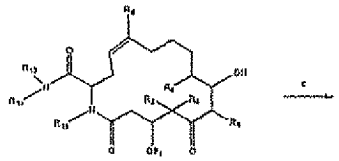
PATENT NO. : 6,605,599 B1
DATED : August 12, 2003
INVENTOR(S) : Gregory D. Vite et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

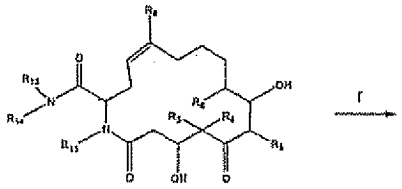
Column 19,
Lines 25-55, the formulae LX, LXI and V should appear:



LX

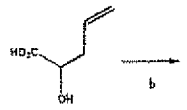


LXI

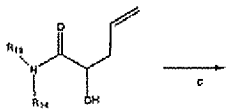


V

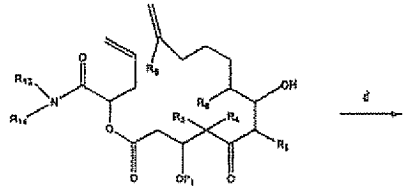
Column 20,
Lines 25-45, the formulae LXII, LXIII and LXIV should appear:



LXII



LXIII



LXIV

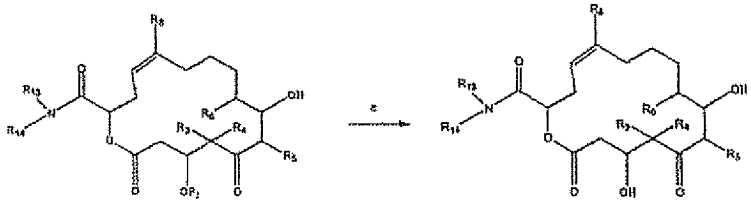
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,605,599 B1
DATED : August 12, 2003
INVENTOR(S) : Gregory D. Vite et al.

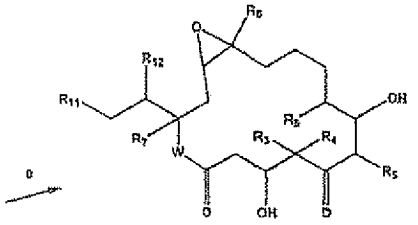
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20 (cont'd),
Line 45-65, formulae LXV and V should appear:

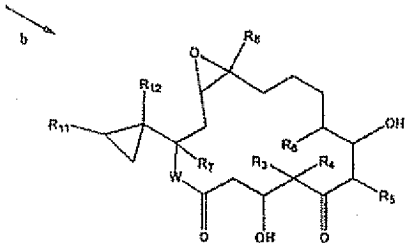


LXV V

Column 22,
Lines 20-45, the following formulae should be canceled from Scheme 14 and inserted instead at col. 21, line 44, under the heading "Scheme 13"and following the compound of formula V:



V



V

Column 21,
Lines 54-55, the text "Scheme 4" should appear -- Scheme 13 --.

Column 25,
Line 52, the text "LXIX" should appear -- LXXIX --.

Column 26,
Line 57, "Y is H,H" should appear -- X is H,H --.
Line 59, the text "LXIX" should appear -- LXXIX --.

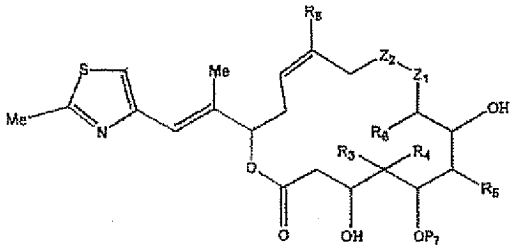
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,605,599 B1
DATED : August 12, 2003
INVENTOR(S) : Gregory D. Vite et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27,
Line 6, "Y is H,H" should appear -- X is H,H --.
Line 7, Insert the text -- Scheme 19 --.
Lines 55-67, the formula "LXXXXVIII" should appear:



LXXXXVIII

Column 28,
Line 57, "W and Y" should appear -- W, X and Y --.
Line 61, "LXXXV" should appear -- LXXXXV --.
Line 63, "LXXXVI" should appear -- LXXXXVI --.
Line 64, "LXXXV" should appear -- LXXXXV --.
Line 66, "LXXXVII" should appear -- LXXXXVII --
Line 67, "LXXXVI" should appear -- LXXXXVI --.

Column 29,
Line 22, "W and Y" should appear -- W, X and Y --.

Column 31,
Line 48, "formula V" should appear -- formula CV --.

Column 37,
Line 4, the text "compound M" should appear -- compound N --.

Column 47,
Line 30, the reference number "V" should appear at line 40, centered under the generic formula.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,605,599 B1
DATED : August 12, 2003
INVENTOR(S) : Gregory D. Vite et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 56,
Line 40 the reference number "V" should appear at line 40, centered under the generic formula.

Signed and Sealed this

Twenty-ninth Day of March, 2005

JON W. DUDAS
Director of the United States Patent and Trademark Office